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# THE REVIEW OF RECENT ADVANCE: "CHEMICAL BEHAVIOUR OF PYRIDOPYRIMIDINE DERIVATIVES AS ANTICANCER AGENT

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## ABSTRACT

Cancer remains a leading cause of mortality worldwide, necessitating the development of novel and effective therapeutic agents. Pyridopyrimidine derivatives have emerged as promising anticancer candidates, exhibiting potent inhibitory activities against various cancer cell lines. This review aims to provide a comprehensive overview of the synthesized compound, their biological evaluation, and clinical potential of pyridopyrimidine derivatives as anticancer agents. We discuss the structural modifications, structure-activity relationships, and mechanistic insights underlying their anticancer properties from previous research. The review also highlights the current status of pyridopyrimidine derivatives in preclinical and clinical trials, as well as their potential combination therapies. Furthermore, we address the challenges and future directions in the development of pyridopyrimidine-based anticancer agents.

## INTRODUCTION

- The following general cancer information is provided globally by the World Health Organization (WHO): Globally, cancer is the biggest cause of mortality. According to the most recent WHO data, it was the reason for 8.2 million deaths, or almost 22% of all deaths unrelated to infectious diseases. The most frequent cancers that cause fatalities each year are those of the stomach, liver, colon, lung, and breast. It is estimated that 13.1 million cancer- related deaths will occur. It is estimated that 13.1 million people would die from cancer worldwide in 2030, a 70% increase over current predictions.[1]
- Cancer is the uncontrollably growing abnormal cells throughout the body. Tumor, malignant, or cancer cells are the terms used to describe these aberrant cells. These cells have the ability to infiltrate healthy tissues. The name of the tissue from which the aberrant cells originated can be useful in recognizing different tumors and the abnormal cells that make up cancer tissue (for example, breast cancer, lung cancer and colon cancer). An alternate term for cancer is a "neoplasm" or a "malignant tumor". One in six fatalities worldwide in 2018 were attributed to cancer, which is the second most common cause of death worldwide with an estimated 9.6 million deaths. Compared to women, who are more likely to acquire breast, colorectal, lung, cervical, and thyroid cancer, men are more likely to develop lung, prostate, colorectal, stomach, and liver cancer.
- Cancer continues to have a financial, psychological, and physical toll on people, families, communities, and global health systems. Many low- and middle-income countries' health systems are ill-equipped to deal with this burden, and many cancer patients worldwide lack access to prompt and effective diagnosis and treatment. The survival rates of many cancer kinds are increasing in nations with developed healthcare systems because early detection is more easily available, treatment is excellent, and survivorship care is provided
- The top three malignancies affecting men, women, and children in the United States are as follows: Men: colorectal, lung, and prostate cancer; women: colorectal, breast, and lung cancer Leukemia and brain tumors Pediatric sand lymphoma Many factors, including age, gender, ethnicity, food, and genetics, might affect the incidence of cancer and its different types. As a result, these many factors have an impact on the incidence and forms of cancer. A wide range of factors, including age, gender, ethnicity, food, and genetics, can affect the incidence of cancer and its many types. As a result, these many factors have an impact on the incidence and forms of cancer.[2]

**Common types of cancer**

- The Global Cancer Observatory has updated its predictions, which show that in 2022, 10 cancer forms would account for over two-thirds of all new cases and deaths globally. Lung cancer is the most frequent cancer, accounting for 2.5 million new cases worldwide, or 12.4% of all new cases. Prostate cancer (1.5 million cases, 7.3%), stomach cancer (970,000 cases, 4.9%), colorectal cancer (1.9 million cases, 9.6%), and female breast cancer (2.3 million cases, 11.6%) were the next in incidence order. Breast cancer is currently the most prevalent malignant tumor among adult females. It is the leading cause of cancer-related death in the globe for women. Breast cancer can still be effectively treated with drug therapy. Lung cancer was the most prevalent cause of cancer-related fatalities (1.8 million, or 18.7% of all cancer- related deaths). Colorectal cancer (900,000, or 9.3%), liver cancer (760,000, or 7.8%), breast cancer (670,000, or 6.9%), and stomach cancer (660,000, or 6.8%) were the next most common causes of cancer-related deaths. Lung cancer is the most common cause of cancer- related death in men worldwide.[3]

**Prevention of cancer**

- Since lifestyle factors are linked to over 80% of cancer cases, adopting healthy habits is crucial for preventing cancer. This involves applying health knowledge to everyday life and providing appropriate encouragement. Everyone agrees that having easier access to information about cancer prevention can raise awareness in the area and have an impact on how pro-health initiatives are created. However, a proper awareness of the subjects' motivation to seek knowledge about health and its causes is necessary for the ultimate assessment of the effectiveness of these kinds of activities. The World Bank's definition of health states that a population's level of education mostly determines its health. A proper education and the subsequent acquisition of pertinent knowledge are contingent upon the effectiveness of the educational system as well as the availability of cutting-edge teaching and learning resources.[4]
- Consuming fruits and vegetables on a regular basis can lower the chance of developing colorectal, rectal, stomach, and breast cancer. The European Prospective Investigation into Cancer and Nutrition (EPIC) has conducted research across Europe and found that eating 400–800 g of fruit and vegetables per day can cut the risk of developing cancers of the mouth, throat, larynx, and esophagus by up to 33%, and lung and stomach cancers by 25%. Fruits and vegetables provide anti-carcinogenic fibers called indoles, phenols, flavonoids, isothiocyanates, and carotenoids, as well as folate and ascorbic acid.[5]

**Activity of heterocyclic compounds:**

- Heterocyclic compounds are mostly composed of atoms other than carbon, with the most prevalent substituents being oxygen, nitrogen, and sulfur. These substances are important in many medical applications because they work well as agents against cancers, bacteria, viruses, and fungi. Heterocycles have several uses, which demonstrates their adaptability.
- Because of their physiological qualities, heterocyclic compounds—which include nitrogen— are essential in medical chemistry and the pharmaceutical business. Nitrogen-based cyclic structures are included in more than 75% of FDA-approved treatments, making them crucial components of novel pharmaceuticals.[6] Heterocyclic compounds based on nitrogen are crucial for treating cancer, and the delivery of medications via nanoparticles enhances pharmacokinetics and minimizes side effects.[7]

**Heteroaryl pyridopyrimidine as anti-cancer agent**

- The distinct structural and biological features of pyridopyrimidine derivatives have attracted a lot of attention in the field of cancer research. These substances are heterocyclic molecules with a fused pyridine and pyrimidine ring that offer a flexible platform for the creation of new medicines. Their potential as efficacious cancer treatments stems from their capacity to inhibit several molecular targets implicated in the progression of cancer.

**Mechanisms of Action**

- Pyridopyrimidine derivatives exhibit anticancer activity through several well-characterized mechanisms:

1. Inhibition of Kinases:

- Many pyridopyrimidine derivatives have been identified as potent inhibitors of tyrosine kinases, such as the vascular endothelial growth factor receptor (VEGFR) and BRAF. By inhibiting these kinases, these compounds disrupt key signaling pathways, thereby inhibiting tumor growth and angiogenesis (Choi et al., 2020). For instance, the compound 4-[(4- methylphenyl)amino]-6-(4-(trifluoromethyl)phenyl)pyrido[2,3-d]pyrimidin-2(3H)-one has shown significant activity against cancer cell lines through this mechanism.

2. Induction of Apoptosis:

- Pyridopyrimidine derivatives can trigger apoptosis in cancer cells by modulating the expression of apoptotic regulators. They promote the release of cytochrome c from mitochondria, leading to the activation of caspases that execute cell death (Lee et al.,

2023). Compounds like 6-(4- (trifluoromethyl)phenyl)-4-(methylthio)pyrido[2,3-d]pyrimidin-2(3H)-one have been shown to effectively induce apoptosis in multiple cancer types.

3. Cell Cycle Arrest

- Certain derivatives induce cell cycle arrest at specific phases, such as G1/S or G2/M, preventing cancer cells from proliferating. This action is often mediated through the inhibition of cyclin- dependent kinases (CDKs), which are essential for cell cycle progression (Kumar et al., 2021). For example, compounds that inhibit CDK2 have been associated with significant anticancer effects by halting cell division in malignant cells.

4. Inhibition of Tumor Metastasis:

- Some pyridopyrimidine derivatives also exhibit anti-metastatic properties by inhibiting cell migration and invasion. This is crucial for preventing cancer spread and improving patient outcomes.[8]

**In-vitro studies of this compound**

- The study includes the results of studies that have been published in the previous few years about the anticancer potential of pyridopyrimidine analogues. For in vitro testing to assess cytotoxicity, cell division, induction of apoptosis, and other relevant endpoints, these studies may employ cancer cell lines. Various in-silico research techniques including as molecular docking, virtual screening, and quantitative structure-activity relationship (QSAR) studies provide valuable understanding of the pharmacological characteristics and molecular interactions of these compounds.[1]

**PYRIDOPYRIMIDINES**

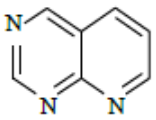
- Mohammed Albratty et al. stress the importance of pyridine and pyrimidine analogues in the development of anticancer drugs, highlighting their wide range of uses and possible therapeutic advantages in different forms of cancer. Based on annulated azaheterocycles, the chemical with polycyclic hetero aromatic compound features significant biological activity. [Heteroaryl pyrimidine Ring As An Anticancer Agent: A Review] This compound's capacity to interact with DNA is what gives it its action. This is as a result of the heteroatoms (nitrogen atoms) they have in their structure.[9] Nitrogen is a heteroatom found in the heterocyclic compounds pyridine and pyrimidine, which have several uses in medical chemistry. In medicinal chemistry, pyrido-pyrimidines are commonly recognized

pharmacophores, which are heterocyclic bicyclic molecules containing nitrogen. Pyridopyrimidines are the structural analogues of biogenic quinazolines and pteridines, formed via the heterocyclic fusion of pyrimidine and pyridine rings.[10]

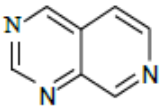
- As possible bioactive compounds, pyridopyrimidines and similar fused heterocycles are of interest. The pyridopyrirmidine moiety found in some significant medications has also sparked interest in creating these kinds of compounds. The chemistry and uses of this family of compounds have been the subject of a vast amount of studies and reviews published in recent years. As putative physiologically active compounds, pyridopyrimidines and related fused heterocyclic rings are of interest. Pyridopyrimidines can exist in six isomer forms. Each of these isomers has a unique biological activity.
- Pyridopyrimidines are fused 6,6-bicyclic heterocycles made up of a pyridine ring fused to a pyrimidine. Based on the location of the nitrogen atom in the pyridine moiety, six isomeric configurations of pyridopyrimidines are possible.[11]

- Pyridopyrimidines and related fused heterocyclic rings are of interest as potential biologically active molecules, in which the pyridopyrimidines exhibit as a six isomer form.These all isomers have different biological activities.[12]

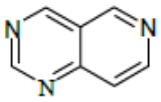
- The six isomers of pyridopyrimidine with their structure are as follow:



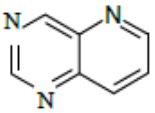
Pyrido[2,3-*d*]pyrimidine



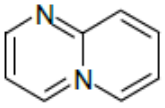
Pyrido[3,4-*d*]pyrimidine



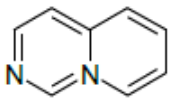
Pyrido[4,3-*d*]pyrimidine



Pyrido[3,2-*d*]pyrimidine



Pyrido[1,2-*a*]pyrimidine



Pyrido[1,2-*c*]pyrimidin

**Pyrido[2,3 - d]pyrimidine derivatives research**

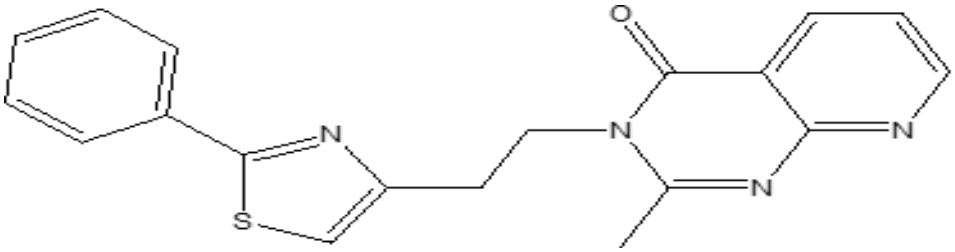
- Rahmani Khajouei et al. Reported 5 synthesized novel pyridopyrimidinon thiozole

derivatives Using thiazole rings, another well-known moiety, they were coupled as biologically active scaffolds to create some intriguing new compounds through a multi-step reaction process. Two human cancer cell lines, MCF-7 and HeLa, were used to investigate the cytotoxic effects of produced chemicals.[13]

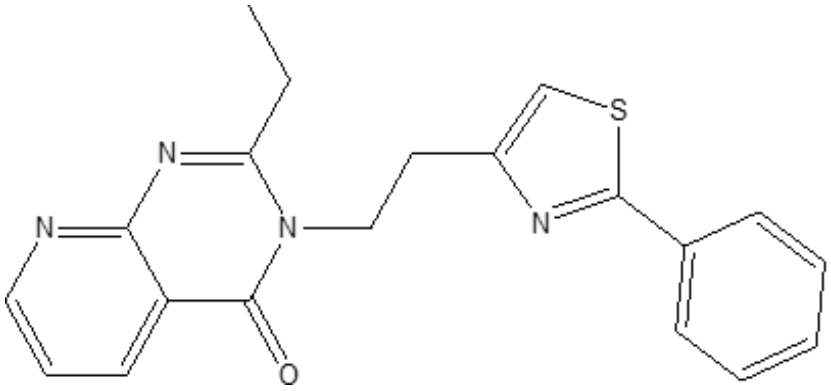
- According to the results of the cytotoxic evaluation, aliphatic substituted compounds demonstrated lower cytotoxic activity, especially on MCF-7 cells, whereas phenyl-and 4-chlorophenyl-substituted derivatives demonstrated the highest cytotoxic activity against both cell lines, particularly the HeLa cells.
- Among all synthesized compound, compound K5, which has a 4-chlorophenyl substituent, showed the greatest efficacy against MCF-7 and HeLa cells, with IC50 values of 119 μM and 15 μM, in that order.

**STRUCTURE**

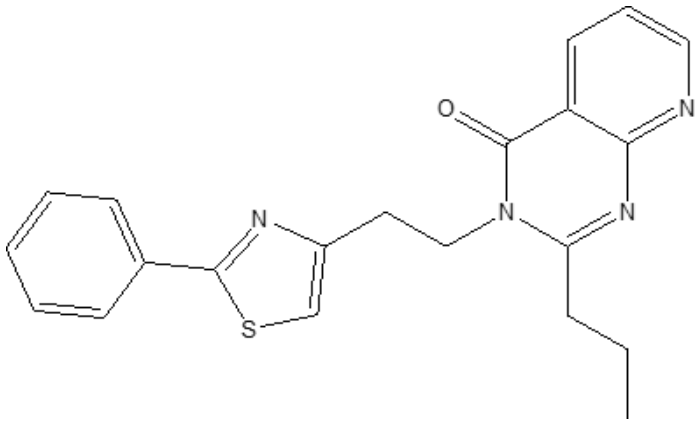
i) 2-Methyl-3-(2-(2-phenylthiazol-4-yl)ethyl) pyrido[2,3-d]pyrimidin-4(3H)-one (K1)



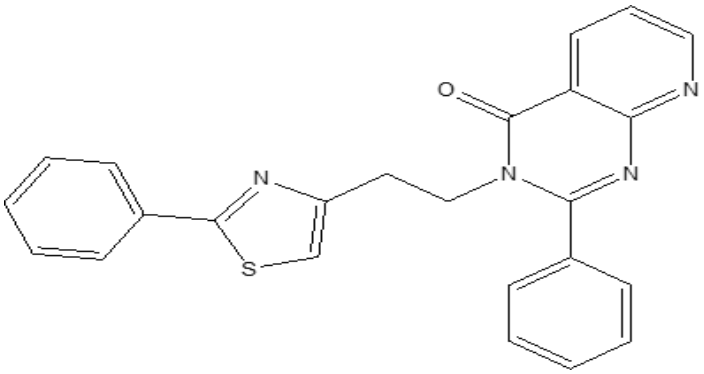

ii) 2-Ethyl-3-(2-(2-phenylthiazol-4-yl)ethyl) pyrido[2,3-d]pyrimidin-4(3H)-one (K2)



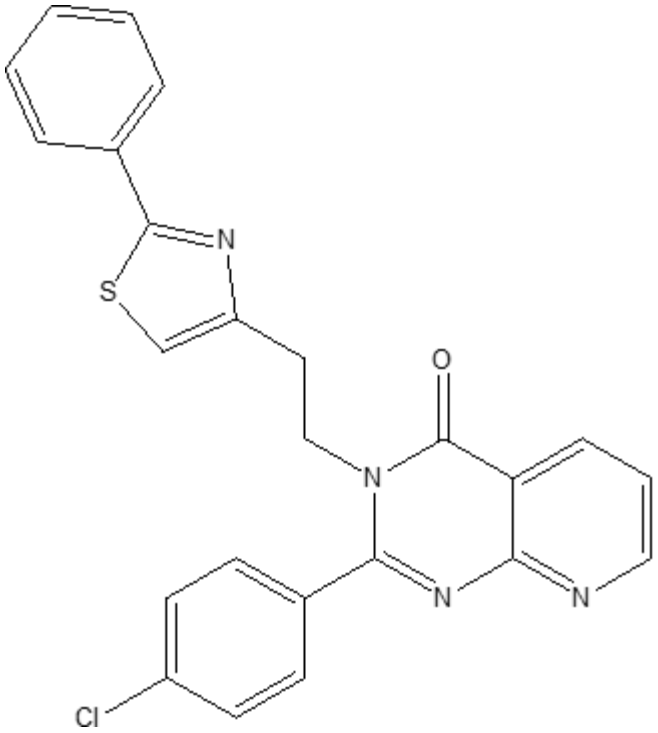

iii) 2-Propyl-3-(2-(2-phenylthiazol-4-yl)ethyl) pyrido[2,3-d]pyrimidin-4(3H)-one (K3)




iv) 2-Phenyl-3-(2-(2-phenylthiazol-4-yl)ethyl) pyrido[2,3-d]pyrimidin-4(3H)-one (K4)




v) 2-(4-Chlorophenyl)-3-(2-(2-phenylthiazol-4-yl)ethyl)pyrido[2,3-d]pyrimidin-4(3H)-one (K5)




➢ Abba et al. Reported synthesis of amide functionalized pyrido[2,3-d]Pyrimidine and

schiff's based derivatives and all compound evaluated for anti cancer activity against four human cancer cell line such as Lung cancer, breast cancer, prostate cancer and cervical cancer.[14]

- All of the synthesized Schiff's base derivatives (5d) and amide functionalized derivatives (7d and 8a) were screened for anticancer activity, according to structure activity relation studies. At micromolar concentrations, nearly all of the compounds demonstrated efficacy against four cancer cell lines. Just three of the compounds—5d, 7d, and 8a—exhibited promising activity out of all of them; the other compounds displayed medium activity. Compound 5d demonstrated the highest potency against all cancer cell lines. Due to the availability of N-attached hydrogen in amide links and its participation in H-bonding (H-attached with an electronegative atom like N), When compared to simple alternatives, the molecule with the trifluoromethyl group exhibits more activity. Additionally, the presence of a thien-2-yl group at position 6 confers a further benefit in enhancing cytotoxic action.

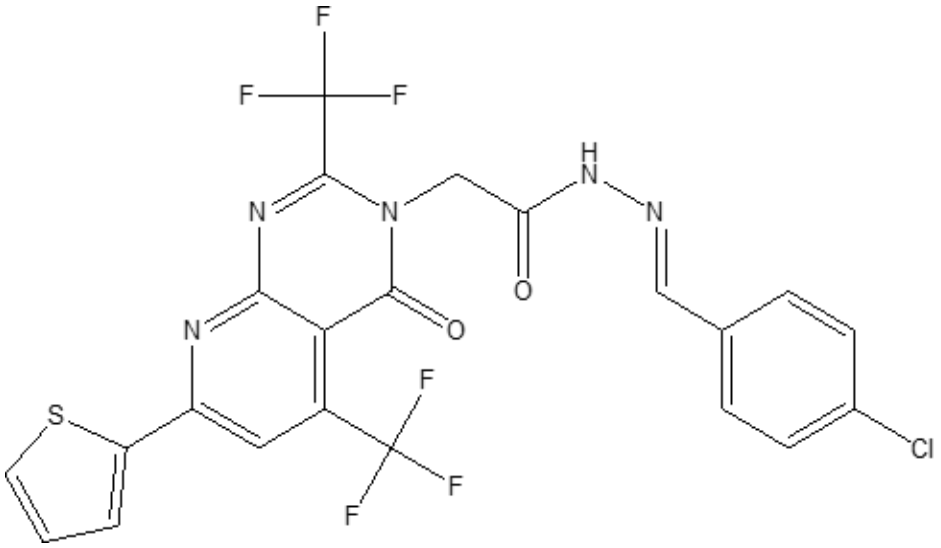
**IC50 Value table**

**Table 1: In vitro cytotoxicity of Schiff base and amide functionalised pyrido[2,3-d]pyrimidine derivatives against four human cancer cell lines.**

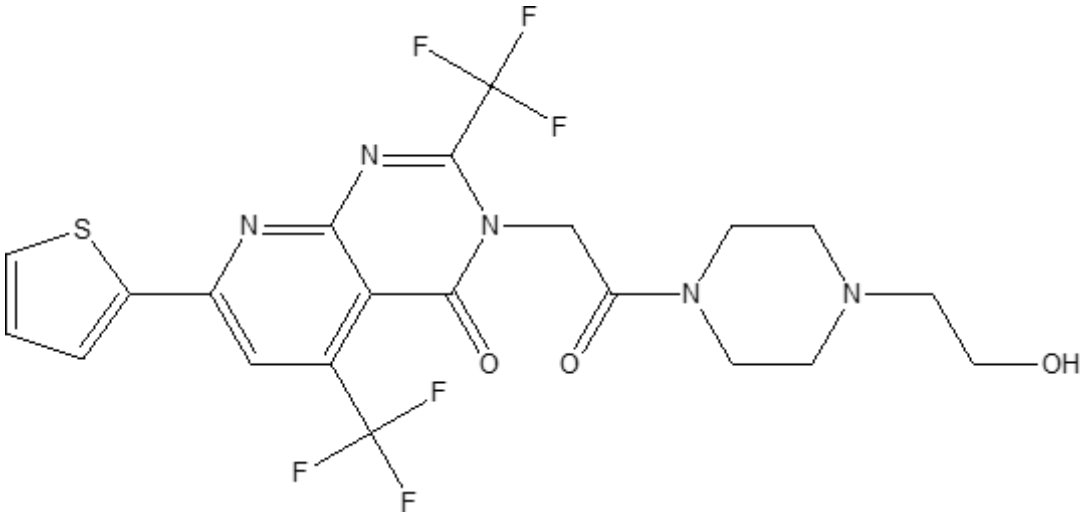
| Compound | IC50 (µM) value | | | |
|---|---|---|---|---|
| | A549 | MCF-7 | DU145 | HeLa |
| 5d | 11.3 | 14.6 | 13.4 | 9.1 |
| 7d | 8.5 | 7.7 | 11.5 | 16.8 |
| 8a | 14.1 | 10.6 | 11.2 | 21.8 |
| 5- flurouracil (std. control) | 1.1 | 1.2 | 1.3 | 1.1 |

**STRUCTURE**

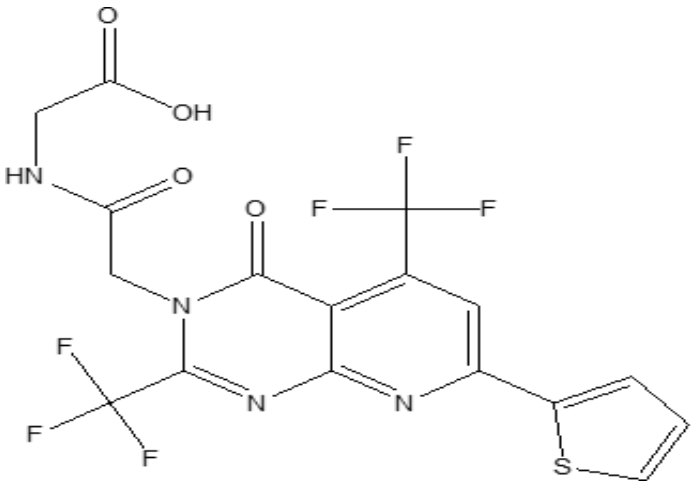
i) E)-N′-(4-Chlorobenzylidene)-2-(4-oxo-7-(thiophen-2-yl)-2,5-bis(trifluoromethyl)pyrido[2,3-d]pyrimidin-3(4H)-yl)acetohydrazide (5d):




ii) 3-(2-(4-(2-Hydroxyethyl)piperazin-1-yl)-2-oxoethyl)-7-(thiophen-2-yl)-2,5-bis(trifluoromethyl)pyrido[2,3-d]-pyrimidin-4(3H)-one (7d):




iii) 2-(2-(4-Oxo-7-(thiophen-2-yl)-2,5-bis(trifluoro-methyl)pyrido[2,3-d]pyrimidin-3(4H)-yl)acetamido)aceticacid (8a):

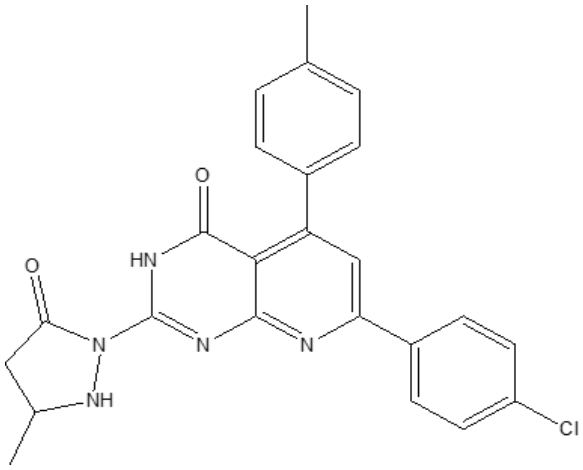


- HebaS. A. et al. reported the synthesis of pyridopyrimidine derivatives (5a), which are tested for their anticancer activity against five cancer cell lines in vitro: HepG-2 for hepatic cancer, PC-3 for prostate cancer, HCT-116 for colon cancer, MCF-7 for breast cancer, and A-549) for lung cancer.

- Comparing compound 5a to standard doxorubicin (IC50: 0.6, 6.8, & 12.8 mM), the compound showed stronger, more potent anticancer activity (IC50: 0.3, 6.6, & 7 mM). In single measurements, the kinase inhibitory assessment of 5a demonstrated encouraging inhibitory activity against three kinases: PDGFR b, EGFR, and CDK4/cyclin D1 at two concentrations of 50 and 100 mM. [15]

**STRUCTURE**

[7(4-chlorophenyl)-2-(3-methyl-5-oxo-2,3-dihydro-1H-pyrazol-1yl)-5-(p-tolyl)- pyrido[2,3-d] pyrimidine -4(3H)-one ]

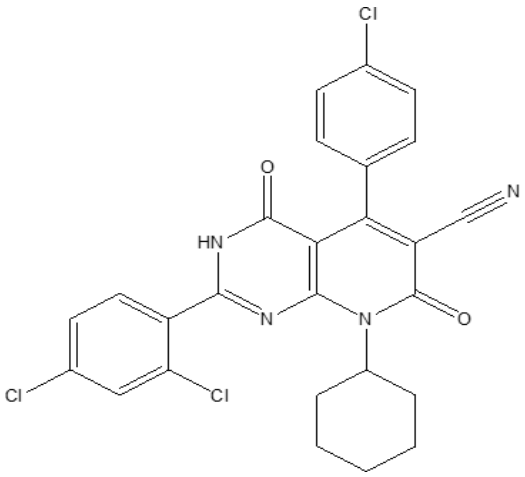



- Derivatives of pyrido[2,3-d]pyrimidines were synthesized and reported by Eman S. Tantawy et al. Compound 4 was one of these derivatives that showed the most potential for killing MCF-7 and HepG2 cells, with IC50 values of 0.57 mM and 1.13 mM, respectively. In contrast to staurosporine (IC50 = 16.7 nM, with 95.6% inhibition), compound 4 exhibited strong PIM-1 kinase inhibition with IC50 values of 11.4 nM, respectively, indicating a 97.8% inhibition. Compound 4 also dramatically halted the cell cycle at the G1 phase and triggered apoptosis in MCF-7 cells. Compound 4 has been confirmed as a potentially effective PIM-1 targeted chemotherapeutic drug for the treatment of breast cancer since then.[16]

- SAR research conveyed The addition of aromatic, hydrophilic hydrogen bond donors and acceptors increased the cytotoxicity, especially in compound 4.

**Structure of compound 4**

i) 5-(4-Chlorophenyl)-8-cyclohexyl-2-(2,4-dichlorophenyl)-4,7-dioxo-3,4,7,8 tetrahydropyrido[2,3-d]pyrimidine-6carbonitrile (4)




- Four different types of malignant cells were used to test the antitumor activity of a synthetic Pyrazol-1-yl pyridopyrimidine derivative, as reported by Fatma MA Krakisha et al. To assess the cytotoxicity, cells from breast cancer (MCF-7), colon cancer (HCT- 166), liver cancer (HepG-2), cervical cancer (HeLa), and normal human lung fibroblast cells (WI-38) were used. With IC50 values of 9.27, 7.69, and 5.91 μM, respectively, relative to standard doxorubicin, compound 5 was found to be the most active against three malignant cells: Hela, MCF-7, and HepG-2. It also demonstrated good inhibition against cyclin dependent kinase (CDK4/cyclin D1) and epidermal growth factor (EGFR) enzymes. [17]
- Based on the structure-activity relationship, derivatives with strong anticancer properties were produced by hybridizing with benzylidine and cyclizing the pyridopyrimidine ring with pyrazole ring.

**STRUCTURE**

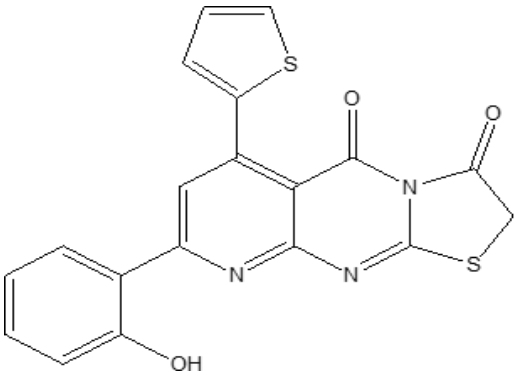

- Shetty et al reported designed and synthesized a range of substituted thiazolo-

pyridopyrimidines as a top scrolling compound and assessed their impact on MCF-7 and MDAMB-231 cell lines using the SRB assay. Remarkably, compounds 4c and 4a exhibited the most promising activity in terms of their IC50 values across both tested cell lines. Selected molecules are evaluated for their anticancer activity against breast cancer by in silico, in vitro models. [18]

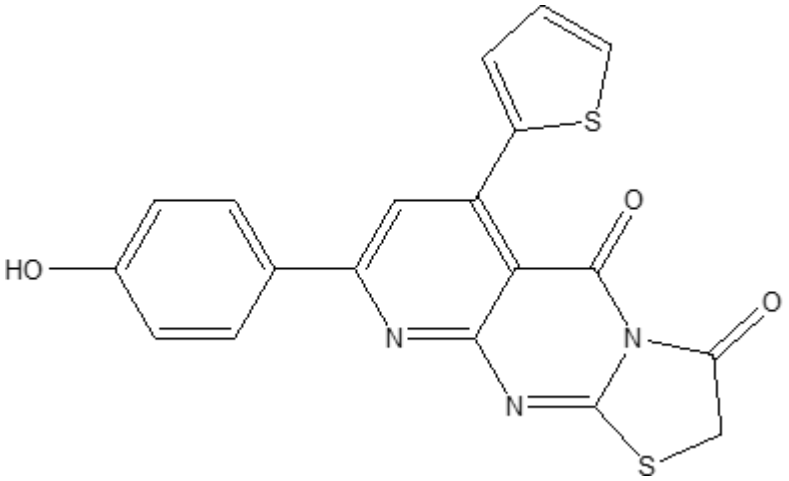
- Compound 4c shows up as a top contender for additional research. According to SAR research, the compound's increased activity may be attributed to the presence of a polar hydroxyl group at the C2 position of the 8-phenyl substitution on the pyridopyrimidine rings. By making structural improvements, the cytotoxic potential could be further enhanced.

**STRUCTURE**

i) 8-(2-hydroxyphenyl)-6-(thiophen-2-yl)-2H-pyrido[2,3-d]thiazolo[3,2-a]pyrimidine- 3,5-dione (4c):




ii) 8-(4-hydroxyphenyl)-6-(thiophen-2-yl)-2H-pyrido[2,3-d]thiazolo[3,2-a]pyrimidine- 3,5-dione (4a):

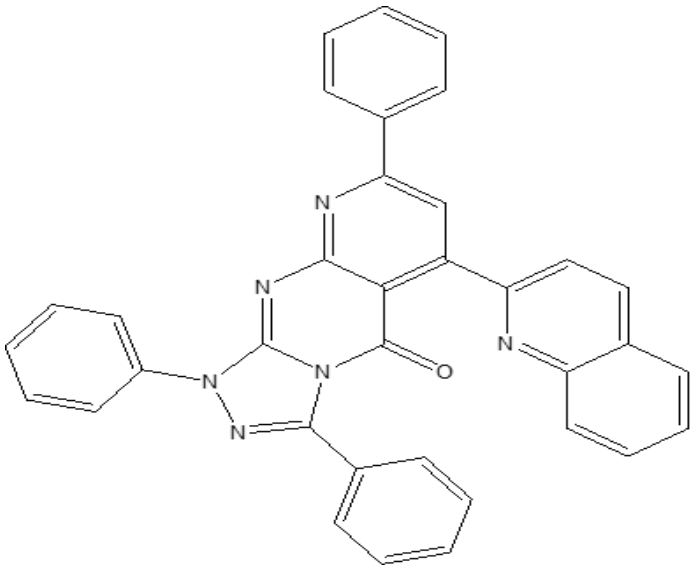



- Abu-Hashem, A.A. et al. state that he came to the conclusion that the interaction between

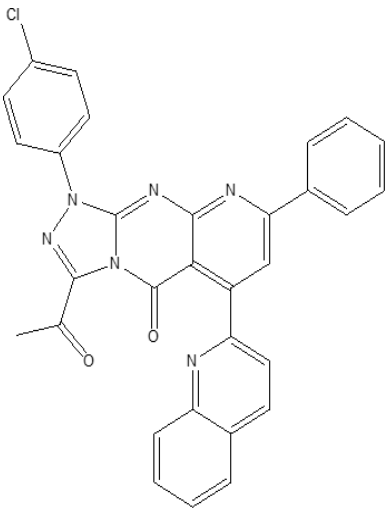
pyrido [2,3-d] pyrimidine derivatives is responsible for the anticancer properties of particular compounds based on the outcomes of biological assays and earlier research. Out of all the compounds that were tested, substituted 6 quinoline pyridotriazolopyrimidinones ( 5a-d) demonstrated encouraging anticancer activity; these compounds could be used in the future to treat a specific range of cancer cells. He has therefore determined that they are promising anticancer agents. Several novel compounds demonstrated significant cytotoxicity against the carcinoma cell lines listed below.[19]

**Structure**

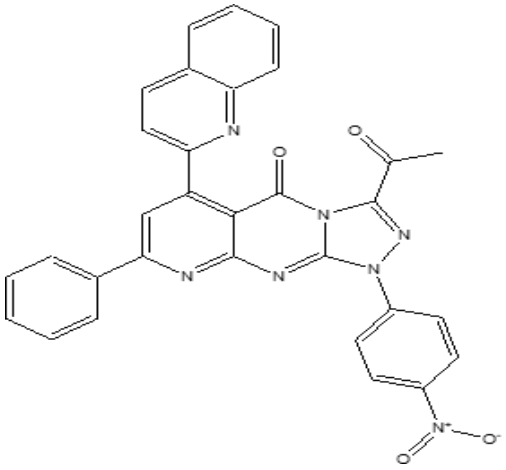
i) 1,3,8-triphenyl-6-(quinolin-2-yl) pyrido [2,3-d] [1,2,4] triazolo [4,3-a] pyrimidin- 5(1H)-one (5a):



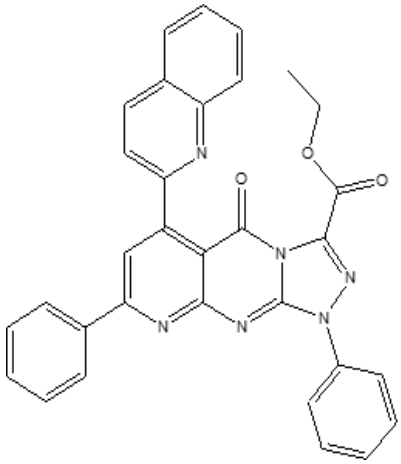

ii) 3-acetyl-1-(4-chlorophenyl)-8-phenyl-6-(quinolin-2-yl) pyrido [2,3-d] [1,2,4] triazolo [4,3-a] pyrimidin-5(1H)-one (5b):



iii) 3-acetyl-1-(4-nitrophenyl)-8-phenyl-6-(quinolin-2-yl) pyrido [2,3-d] [1,2,4] triazolo [4,3-a] pyrimidin-5(1H)-one (5c):



iv) ethyl 5-oxo-1,8-diphenyl-6-(quinolin-2-yl)-1,5-dihydropyrido [2,3-d] [1,2,4] triazolo [4,3-a] pyrimidine-3-carboxylate (5d):



- E. M. AbedelRehim and M. AbdEllatif et al. reported in the Journal of Heterocyclic Chemistry that the anticancer activity of the ten synthesized pyrido-pyrimidine derivatives was assessed on human cancer cell lines that represented liver and colon cancer. Compounds 6b, 7b, 8b, and 9b can be recommended as strong candidates for colon and liver cancer drugs. The inhibitory activities against colon carcinoma cells (HCT-116) and hepatocellular carcinoma cells (HepG-2) were tested using different concentrations of the samples (50, 25, 12.5, 6.25, 3.125, and 1.56µg).[20]

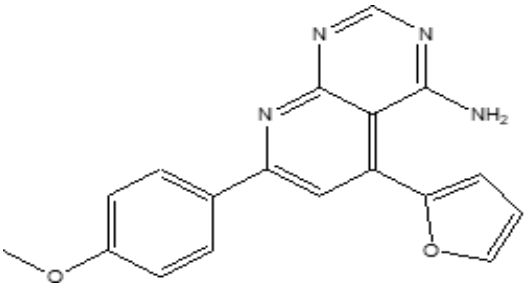
**IC50 Value table**

**Table 2: IC50(µg) values of pyrido-pyrimidine derivatives after 24h continuous exposure of tumor cell lines.**

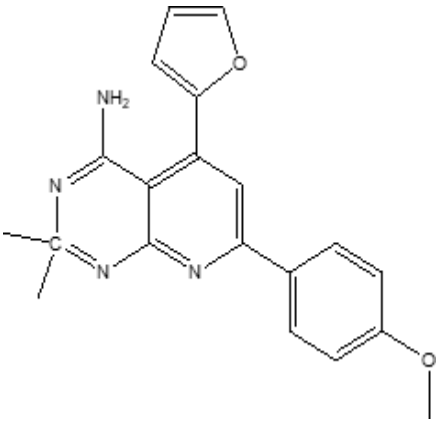
| Compound | IC50 (µg) value | |
|---|---|---|
| | HCT-116 | HepG-2 |
| 6d | 4.12 | 6.83 |
| 7d | 6.81 | 5.99 |
| 8d | 3.55 | 8.29 |
| 9d | 4.82 | 10.12 |
| Vinblastine standard | 2.78 | 5.11 |

**Structure**

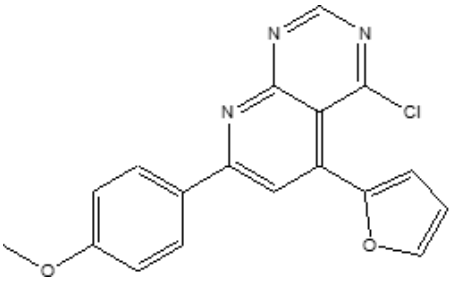
i) 5-(Furan-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidin 4-ylamine 6b:



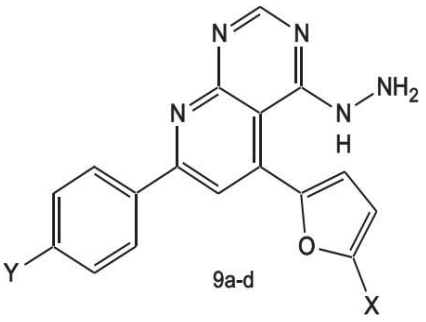

ii) 5-(Furan-2-yl)-2-methyl-7-(4-methoxyphenyl)-2-methylpyrido [2,3-d]pyrimidin-4-ylamine 7b:




iii) 4-Chloro-5-(furan-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d] pyrimidine 8b:



iv) 5-(Furan-2-yl)-7-(4-methoxyphenyl)pyrido[2,3-d]pyrimidin 4-yl)hydrazine 9b:




- Alkyl-substituted pyrido[2,3-d]pyrimidine derivatives have been described by Kumar et al. as anticancer agents. The anticancer properties of all the synthesized compounds were evaluated against four distinct human cancer cell lines: PC-3 (prostate cancer), MCF-7 (breast cancer), Hep G2 (liver cancer), and HCT 116 (colorectal cancer). Compounds 1n and 2j, out of all the synthesized compounds, showed outstanding anti- cancer activity against every cancer cell line, with IC50 values listed in the table.[21]

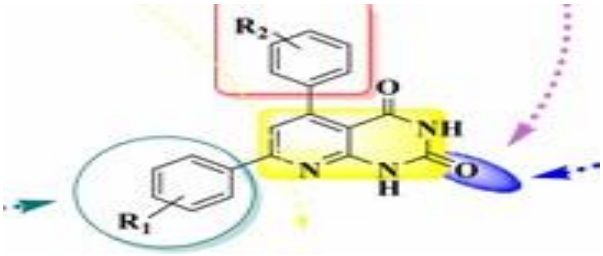
**IC50 Value Table**

**Table 3: IC50 values in (nM) for compound 1n & 2j with standard control raltitrexed.**

| **Compound** | **IC50 (**nM) value | | | |
|---|---|---|---|---|
| | HCT 116 (colorectal cancer) | MCF-7 (breast cancer) | Hep G2 (liver cancer) | PC-3 (prostate cancer) |
| **1n** | 1.98±0.69 | 2.18±0.93 | 4.04±1.06 | 4.18±1.87 |
| **2j** | 1.48±0.86 | 3.18±0.79 | 3.44±1.51 | 5.18±1.85 |
| Raltitrexed | 1.07±1.08 | 1.98±0.72 | 1.34±1.01 | 3.09±0.96 |

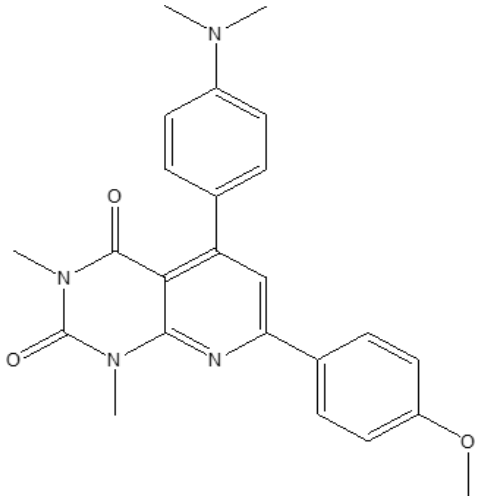
- Electron-donating groups at positions R and R1 in the synthesized compounds demonstrated strong activity against all tested cell lines, according to a structure- activity relationship relationship. Compared to compounds substituted at ortho and meta positions, compounds substituted at the para position had a better IC50. According to Kumar et al.'s findings from 2023, the pyridogrido[2,3-d]pyrimidine pharmacophore was necessary for anticancer activity.

**Image of SAR**

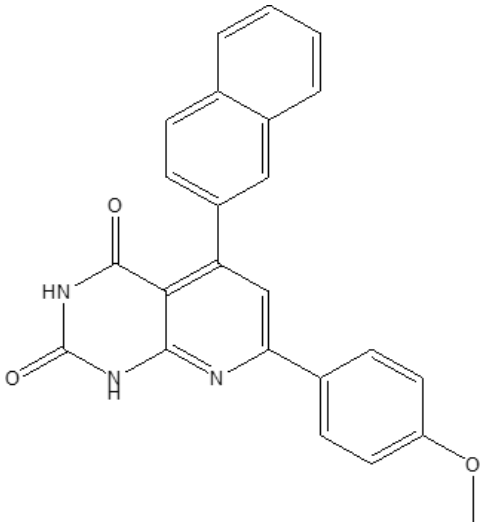


**Structure**

i) 5-(4-(dimethylamino)phenyl)-7-(4-methoxyphenyl)-1,3 dimethylpyrido[2,3-d]pyrimidine-2,4(1 H,3 H)-dione 2 (j) :



ii) 7-(4-methoxyphenyl)-5-(naphthalen-2-yl)pyrido[2,3-d] pyrimidine-2,4(1 H,3 H)- dione 1 (n):



- According to Abbas, George, Samir, Aref, & Abdel-Aziz et al. Novel tricyclic and bicyclic pyridopyrimidines were synthesized and evaluated for their cytotoxicity against the breast cancer cell lines MCF-7, the lung cancer cell line A549, the prostate cancer cell line PC-3, and the normal fibroblasts WI-38. They demonstrated moderate to strong activity, with compounds 6b, 6e, 7b, and 8d demonstrating superior activity against the tested cell lines at the submicromolar level when compared to doxorubicin. Compounds 6b and 8d activated caspase- 3 (in PC-3), Bax, and p53, down-regulated Bcl2, and inhibited CDK4/6 to cause apoptosis in PC-3 and MCF-7, respectively. Compound 8d inhibited CDK6 with an IC50 of 726.25 nM, whereas compound 6b directly inhibited it at 115.38

nm.[22]

**IC50 value Table**

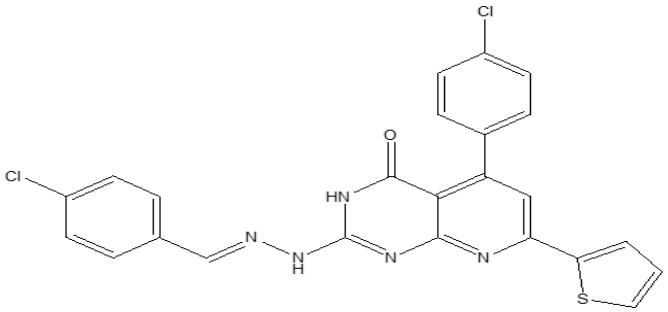
**Table 4: IC50 values in (µM) for compound 6b, 6e, 7b & 8d with reference standard doxorubicin.**

| Compound | IC50 (µM) value | | | |
|---|---|---|---|---|
| | MCF-7 | A-549 | PC-3 | WI-38 |
| **6b** | 1.59 ± 0.82 | 2.48 ± 0.921 | 0.01 ±0.003 | >100 |
| **6e** | 0.06 ± 0.006 | 0.08 ± 0.005 | 0.42 ± 0.03 | >100 |
| **7b** | 4.27 ± 0.004 | 1.87 ± 0.42 | 0.03 ±0.001 | 78.0 ± 12.38 |
| **8d** | 0.01 ± 0.001 | 1.69 ± 0.86 | 1.37 ± 0.92 | >100 |
| **doxorubicin** | 0.04 ± 0.008 | 0.06 ± 0.009 | 0.09 ±0.007 | >100 |

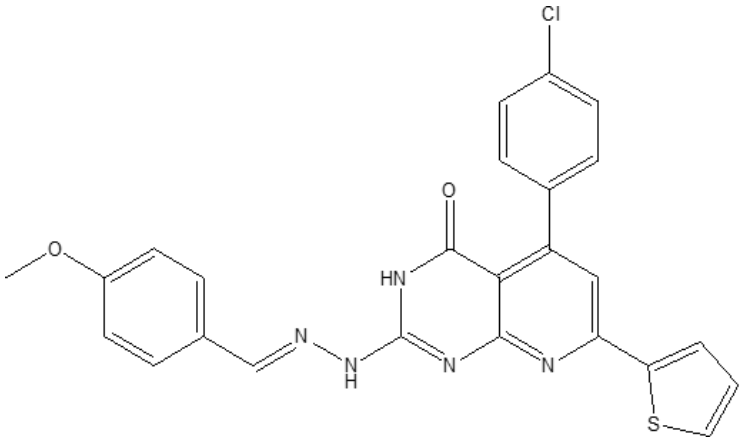
- According to the structure-activity relationship, the substituted derivatives particularly the p-OCH3 derivative—exhibited better submicromolar activity than the unsubstituted one. Because of its increased lipophilicity, the ethyl carboxylate tricyclic triazolo derivative (7b) showed more activity than its acetyl analog. When compared to doxorubicin, the compound with the highest potency was 4-methylbenzylidene derivative 8d, as the presence of electron-donating moieties was preferred for the activity. A range of activity, from moderate to high potency, was observed upon substitution with electron-donating groups such as 4-methyl or 4-methoxy 6e.

**Structure**

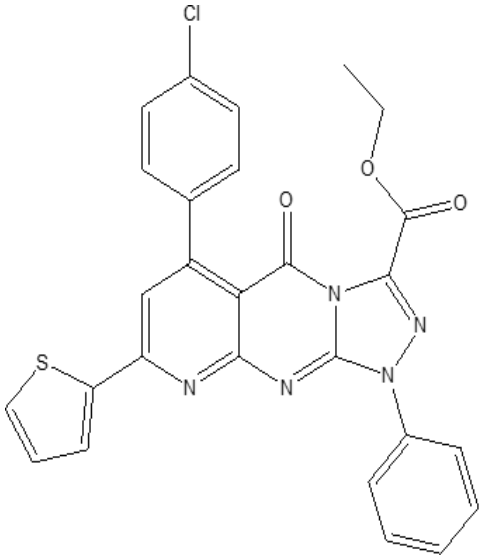
i) 2-[2-(4-Chlorobenzylidene)hydrazinyl]-5-(4-chlorophenyl)-7-(thiophen-2- yl)pyrido[2,3-d]pyrimidin-4(3H)-ones (6b)



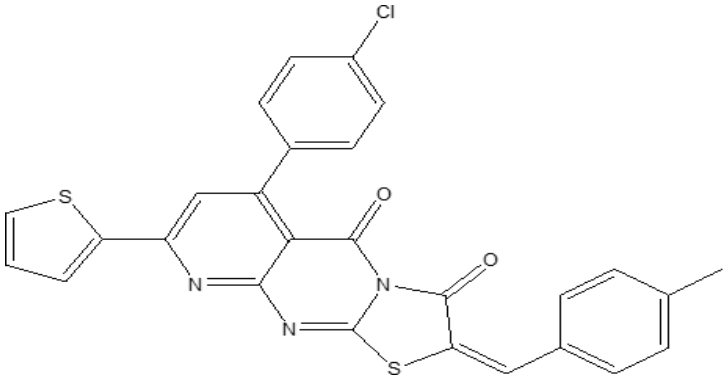

ii) 5-(4-Chlorophenyl)-2-[2-(4-methoxybenzylidene)hydrazinyl]-7-(thiophen-2- yl)pyrido[2,3-d]pyrimidin-4(3H)-one(6e)




iii) Ethyl 6-(4-chlorophenyl)-5-oxo-1-phenyl-8-(thiophen-2-yl)-1,5- dihydropyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidine3-carboxylate(7b)




iv) 6-(4-Chlorophenyl)-2-(4-methylbenzylidene)-8-(thiophen-2-yl)-5H-pyrido[2,3-d]thiazolo[3,2-a]pyrimidine-3,5(2H)-dione (8d)




- A series of novel pyrido[2,3-d]pyrimidine derivatives linked to different substitutions at positions 2 and 5 were synthesized and docked into the active site of CDK2, as reported

by Jamelah S. Al-Otaibi et al. They claim Compounds 6c, 8d, and 9c can be used as a lead compound for additional optimization because they demonstrated excellent selectivity towards CDK2 and very good activity against breast and colon cancer. According to the modeling studies, the derivatives with SCH3 group were more active than the derivatives with C=S, and the derivatives with sulfanilamide group were the most active.[23]

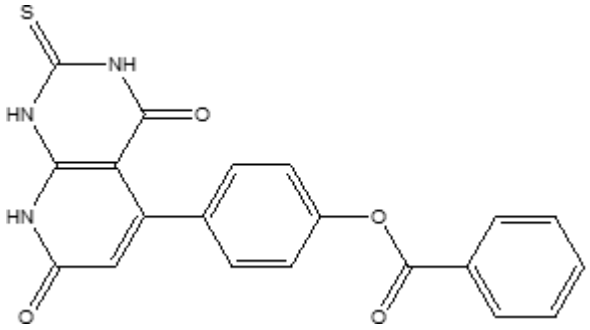
**IC 50 value table**

Table 5 : IC50 values in (µM) for compound 6c, 8d & 9c.

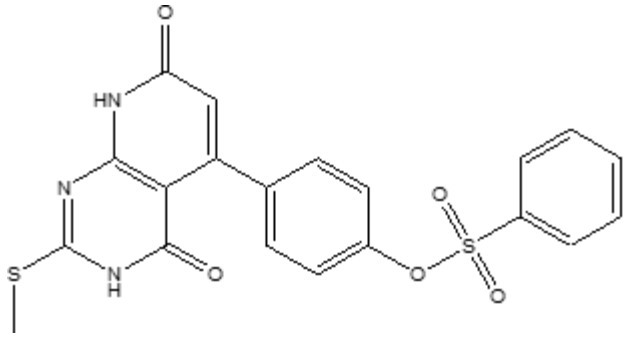
| **Compound** | **IC50** (µM) | |
|---|---|---|
| | MCF-7 | CaCO2 |
| **6c** | 7.4 | **18.0** |
| **8d** | 5.5 | **4.2** |
| **9c** | 6.4 | **3.2** |

**Structure**

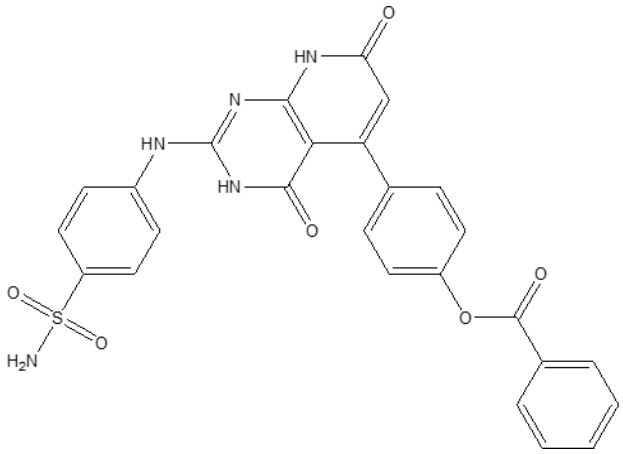
i) 4-(4,7-dioxo-2-thioxo-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidin-5-yl)phenyl benzoate 6c




ii) 4-(2-(methylthio)-4,7-dioxo-3,4,7,8-tetrahydropyrido[2,3-d]pyrimidin-5yl)phenyl benzenesulfonate 8d



iii) 4-(4,7-dioxo-2-((4-sulfamoylphenyl)amino)-3,4,7,8-tetrahydropyrido[2,3 d]pyrimidin-5-yl)phenyl benzoate 9c




- According to Magda A. Abdallah et al., 20 pyridotriazolopyrimidinones were tested for their anticancer potential against the MCF-7 and HepG2 cancer cell lines. and he disclosed that when compared to doxorubicin, the typical reference medication, compounds 7d and 9 exhibit encouraging activity.

- Structure, activity, and relationship explain that Compound 9, which has a methyl group at position 3 in the triazole ring, is the most reactive. Compounds 7b and 7d (containing methyl and methoxy groups) have an additional aryl group at position 3 of the triazole ring that donates electrons, increasing their potency as antitumor agents. Position 3 of the triazole ring contains an electron-withdrawing acetyl or ester group, which significantly reduced the compounds' inhibitory activity against the cancer cell lines MCF-7 and HepG2.[24]

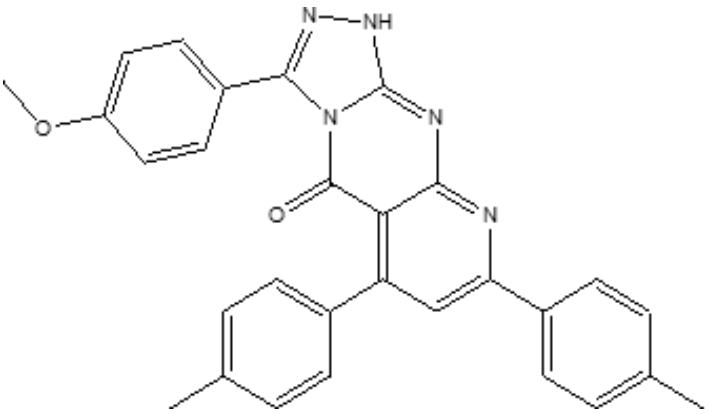
**IC50 value**

**Table 6: IC50 values in (µg/ml) for compound 7d & 9 with standard control doxorubicin.**

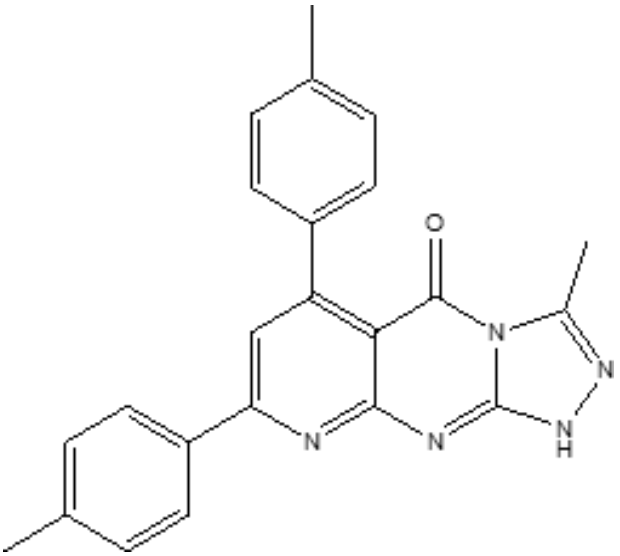
| Compound | IC50 values (µg/mL) | |
|---|---|---|
| | MCF-7 | HepG2 |
| 7d | 7d 4.8 ± 1.91 | 2.7 ± 1.42 |
| 9 | 9 3.1 ± 1.50 | 2.5 ± 1.52 |
| Doxorubicin | 0.51 ± 0.04 | 0.45 ± 0.07 |

**Structure**

i) 3-(4-Methoxyphenyl)-6,8-di-p-tolylpyrido[2,3-d][1,2,4]triazolo [4,3-a]pyrimidin-5(1H)- one (7d).




ii) 3-Methyl-6,8-di-p-tolylpyrido[2,3-d][1,2,4]triazolo[4,3-a] pyrimidin-5(1H)-one (9).




- According to Sobhi M. Gomha et al., a number of novel thiadiazoles and pyrazolinones bearing pyridopyrimidine moiety were synthesized. The Sulforhodamine-B (SRB) assay was used to screen the target thiazoles for antiproliferative activity against the human breast cancer MCF-7 cell line, with tamoxifen serving as the reference medication.
- Compounds containing COOEt substituents at position 5 exhibit strong in vitro inhibitory activity (7f). The antitumor activity of the 1, 3, 4-thiadiazole ring is increased by the addition of an electron-donating group (methyl) at position C4 of the phenyl group at position 4.(7b). The arylhydrazo group (ArNHN=) exhibits greater activity than the arylidene group (Ar-CH=) for the substituent at position 4 (13). The phenyl ring's C4 electron-donating group (methyl) increases the antitumor activity (13b).[25]

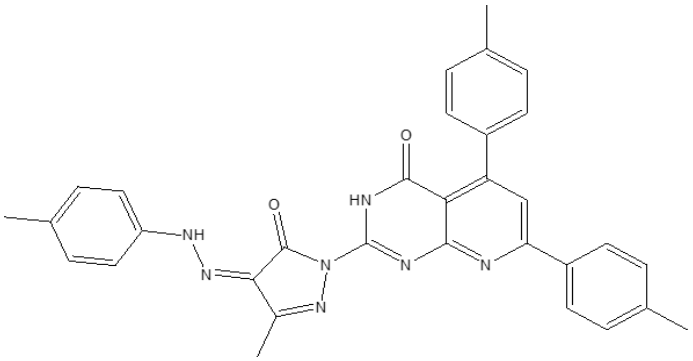
**IC50 value table**

**Table 7: IC50 values in (µg/ml) for compound 7b, 7f &13b with standard tamoxifen.**

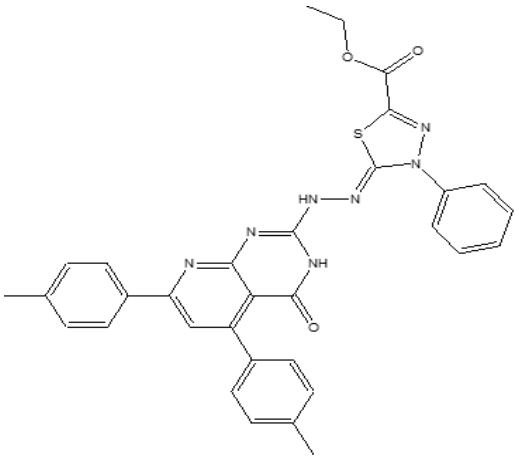
| Compound | IC50 values (µg/ml) for MCF-7 cell line |
|---|---|
| 7b | 9.7 ± 1.19 |
| 7f | 8.7 ± 1.28 |
| 13b | 8.1 ± 1.7 |
| Tamoxifen | 8.1 ± 1.23 |

**Structure:**

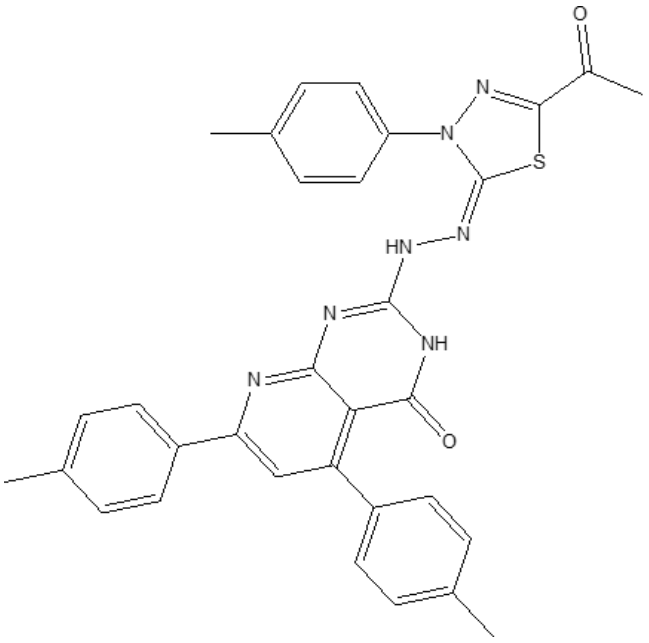
i) 2-(3-methyl-5-oxo-4-(2-(p-tolyl) dihydro-1H-pyrazol-1-yl)-5, hydrazono)-4, 7-di-p-tolylpyrido 5 [2,3-d] pyrimidin-4 (3H)-one (13b)




ii) Ethyl 5-(2-(4-oxo-5, 7-di-p-tolyl-3, 4-dihydropyrido [2,3-d] pyrimidin-2-yl) hydrazono)-4-phenyl-4, 5-dihydro-1, 3, 4 thiadiazole-2-carboxylate (7f)




iii) 2-(2-(5-Acetyl-3-(p-tolyl)-1, 3, 4-thiadiazol-2 (3H)-ylidene) hydrazinyl)-5, 7-di-p-tolylpyrido [2,3-d] pyrimidin-4 (3H) one (7d)




- Basant Farag et al. reported anti-cancer agents in vitro against three cell lines, comparing them to 5-FU, MTX, and DOX. The antiproliferative activity of these compounds was assessed against human cell lines, namely HEPG-2, HCT-116, and MCF-7, which represent human hepatocarcinoma and colon cancer, individually. Following compound 6d, compound 6g, and compound 6b with great affinity to bind with topoisomerase II active and allosteric sites, compound 6a showed the strongest activity against these cell lines.[26]

**IC50 value table**

**Table 8: IC50 values in (µM) for compound 6b, 6d & 6g with reference standard 5-FU, MTX & DOX.**

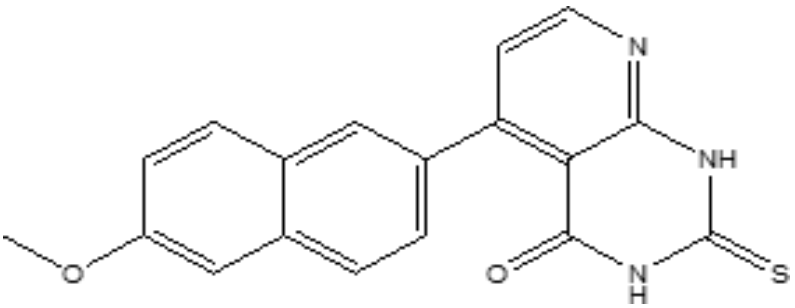
| Compound | In vitro Cytotoxicity IC50 (µM) | | |
|---|---|---|---|
| | HePG2 | HCT-116 | MCF-7 |
| **6b** | 6.91±0.4 | 7.81±0.5 | 4.50±0.2 |
| **6d** | 15.29±1.3 | 9.32± 0.8 | 13.95±1.2 |
| **6g** | 8.66±0.6 5. | 5.93±0.4 | 7.50±0.5 |
| 5-FU | 8.09±0.5 | 5.22±0.3 | 3.67±0.1 |
| MTX | | 9.25±0.7 | 25.32±1.6 |
| DOX. | 4.50±0.2 | 5.23±0.3 | 4.17±0.2 |

- According to Mardia T. El Sayed et al., produced pyrido[2,3-d]pyrimidines are tiny compounds that can prevent cancer cells from tyrosine kinase. With an inhibition % value of 81.72 at a concentration of 25 nM and an IC50 of 8.4 nM, which is quite close to the reference medication Sorafenib, compound 9b emerged as the most active one among the synthesized series.[27]

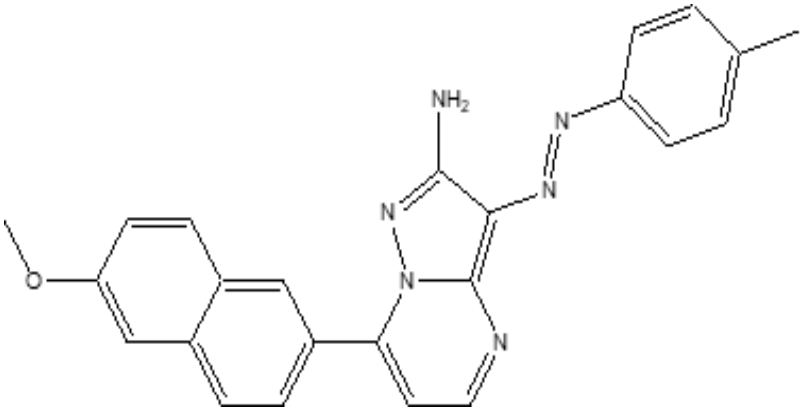
- Compounds 9b, 6f, and 13 are the most active derivatives from the in-vitro cytotoxicity test; these compounds showed the highest activity against the chosen cell lines, and their activities are very similar to those of sorafenib, the commonly used medication.

**Structure:**

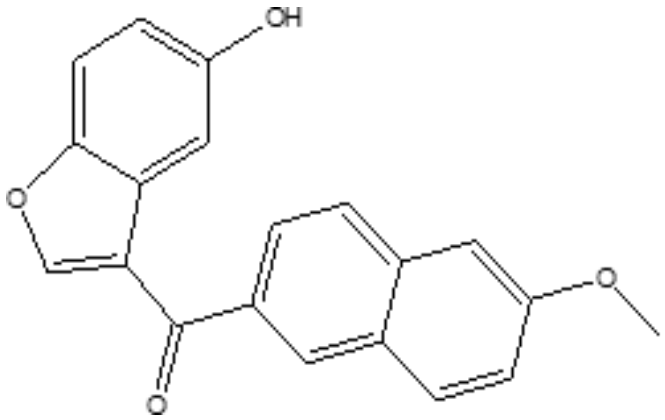
i) 5-(6-Methoxy-naphthalen-2-yl)-2-thioxo-2,3-dihydro-1H-pyrido[2,3-d]pyrimidin-4-one (9b):




ii) 7-(6-Methoxynaphthalen-2-yl)-(3-p-tolyldiazenyl)pyrazolo[1,5-a]pyrimidin-2-amine (6f):




iii) (5-Hydroxy-benzofuran-3-yl)-(6-methoxy-naphthalen-2-yl)-methanone(13):




**Pyrido(1,2-a) pyrimidine derivatives research:**

- In a study published in the journal Cancer Research, author R. Desari designed and

synthesized novel 1,3,4-oxadiazole functionalized pyridopyrimidine derivatives and assessed their anticancer activity against four human cancer cell lines: MCF7 - Breast cancer (HTB-22); HeLa - Cervical cancer (CCL-2); COLO 205 - Colon cancer (CCL-222); and HepG2- Liver cancer (HB8065). Out of all the compounds, compounds 7d and 7k had encouraging action, whereas the other compounds displayed moderate activity. Studies on the link between structure and activity found that oxadiazole derivative-containing trifluoromethyl and methoxy groups exhibited good activity.[28]

- By measuring the in vitro growth inhibition of tumor cell lines in 96-well plates through cell-mediated reduction of tetrazolium salt to water-insoluble formazan crystals, 5-fluorouracil was used as a reference to test the cytotoxicity of the compounds.

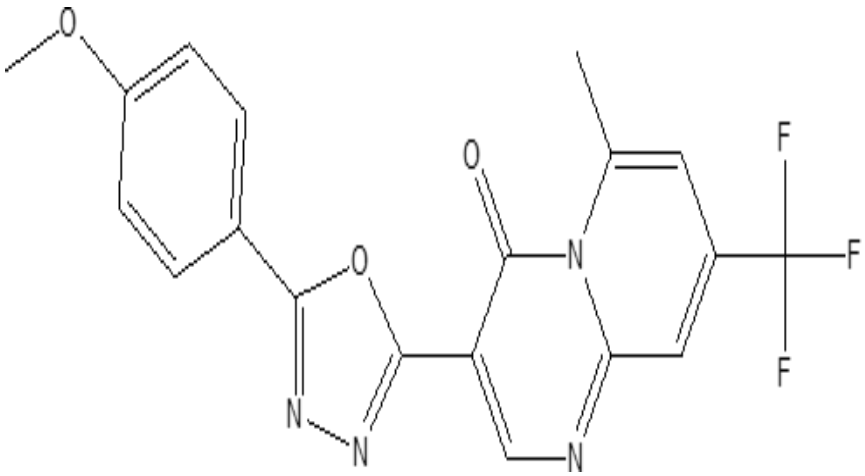
**IC50 value Table**

**Table 9: IC50 values in (µg/ml) for compound 7d & 7k with standard control 5-fluorouracil.**

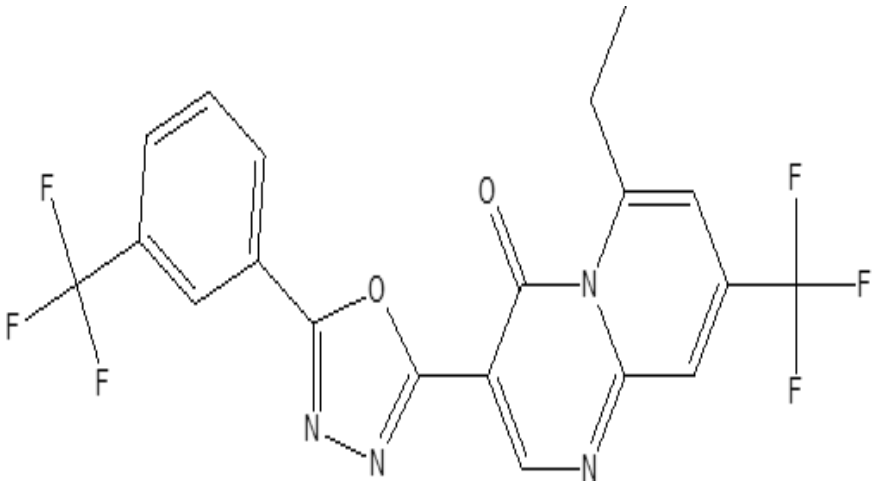
| Compound | IC50 values (µg/ml) | | | |
|---|---|---|---|---|
| | HeLa (Cervical cancer) | COLO 205 (Colon cancer) | HepG2 (Liver cancer) | MCF7 (Breast cancer) |
| **7d** | **16.2 ± 0.21** | **23.4 ± 0.35** | **22.6 ± 0.13** | **19.9 ± 0.36** |
| **7k** | **14.3 ± 0.31** | **28.9 ± 0.61** | **21.5 ± 0.11** | **19.5 ± 0.35** |
| 5-fluorouracil (std. Control) | **1.8 ± 0.09** | **1.9 ± 0.11** | **1.7 ± 0.08** | **1.8 ± 0.07** |

**STRUCTURE**

1. 3-(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl)-6-methyl-8-(triuoromethyl)-4H-pyrido[1,2-a]pyrimidin-4-one (7d):



2. 6-Ethyl-8-(tri uoromethyl)-3-(5-(3-(tri uoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)-4H- pyrido[1,2-a]pyrimidin-4one (7k):




- In Asian journal of chemistry M. kumara swamy et al. reported synthesized The pyridopyrimidine carbohydrazide derivatives and carboxamide functionalized derivatives and were tested for anticancer activity among four human cancer cell lines such as HeLa - cervical cancer (CCL-2); COLO 205 - colon cancer (CCL-222); HepG2 - liver cancer (HB- 8065); MCF7 breast cancer (HTB-22). 5-Fluorouracil used as standard control. Among all the synthesized compounds, some compounds showed activity up to the MIC concentration of 118.7 µM, Compounds 7a and 7b showed the promising activity.[29]

- SAR data explain that carboxamide functionalized derivatives were tested for potent anticancer activity due Free hydrogen of amide functional group, participated in H-bonding (H-attached with electronegative atom like N).

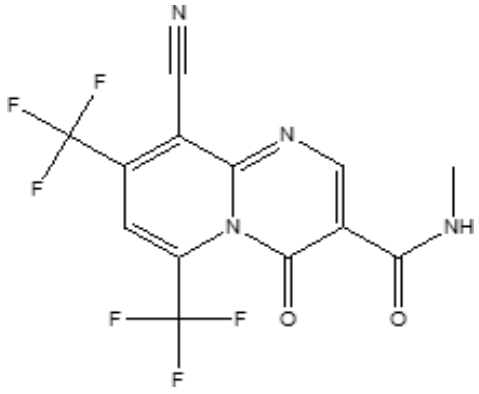
**IC 50 value table**

**Table 10: IC50 values in (µM) for compound 7a & 7b with reference standard 5-FU.**

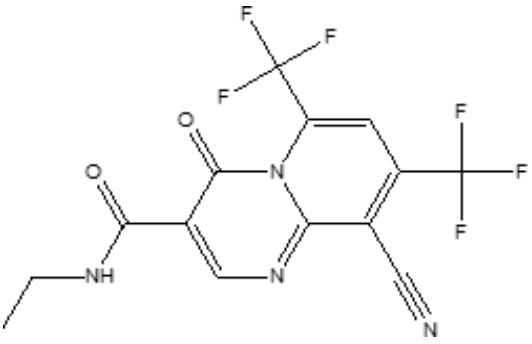
| Compound | IC50 values (µM) | | | |
|---|---|---|---|---|
| | HeLa | COLO205 | HepG2 | MCF7 |
| **7a** | 21.5 ± 0.16 | 32.2 ± 0.16 | 21.8 ± 0.23 | 19.2 ± 0.22 |
| **7b** | 23.1 ± 0.31 | 36.8 ± 0.26 | 29.5 ± 0.18 | 18.7 ± 0.38 |
| 5- Fluorouraci l (std. Control) | 1.8 ± 0.09 | 1.9 ± 0.11 | 1.7 ± 0.08 | 1.8 ± 0.07 |

**Structure of 7a and 7b:**

i) 9-Cyano-N-methyl-4-oxo-6,8-bis(trifluoromethyl)-4H pyrido[1,2-a]pyrimidine-3-carboxamide (7a):




ii) 9-Cyano-N-ethyl-4-oxo-6,8-bis(trifluoromethyl)-4H pyrido[1,2-a]pyrimidine-3-carboxamide (7b):




- Using 5-fluorouracil as a standard, Gautham S. Kumar et al. synthesized Pyrido[1,2-a]pyrimidine-3-carboxamide derivatives compounds 6h–k and n, which were then screened against four human cancer cell lines, including DU145 (prostate cancer HTB-81), A549 (lung cancer CCL-185), SiHa (squamous cell carcinoma HTB-35), and MCF-7 (breast cancer HTB-22). The IC50 values of the test compounds for 24 hours on each cell line were computed and given in a table.[30]

**IC50 Value table:**

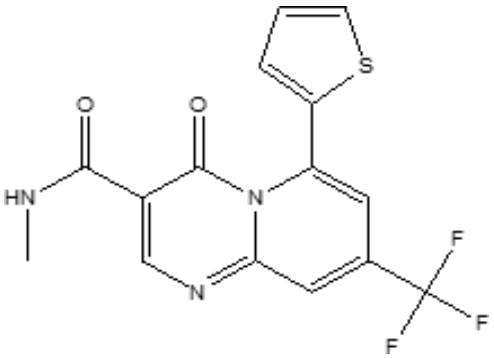
**Table 11: IC50 values in (µM) for compound 6h to 6n.**

| Compound | IC50 values in (µM) | | | |
|---|---|---|---|---|
| | DU145 | A549 | SiHa | MCF-7 |
| **6h** | 5.8±0.16 | 9.5±0.21 | 8.6±0.22 | 7.2±0.15 |
| **6i** | — | 3.2±0.12 | 5.6±0.26 | 6.2±0.32 |
| **6j** | — | 3.6±011 | 9.5±0.14 | 10.8±0.32 |
| **6k** | 5.3±0.12 | 7.6±0.18 | 8.1±0.27 | 10.4±0.18 |
| **6n** | — | 6.1±0.22 | 8.4±0.14 | 11.6±0.34 |

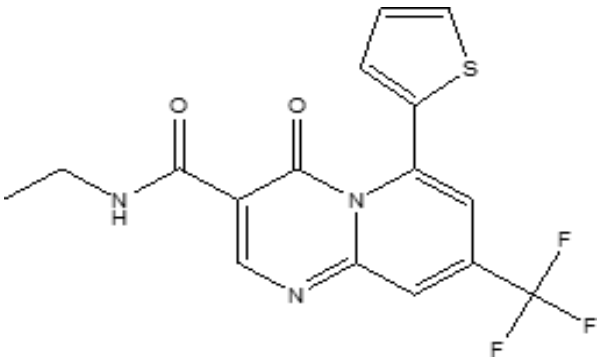
- When compared to compounds 6h–n with a R=phenyl group at the sixth position, the compounds with the R=thien-2yl group at that position generally displayed better activity. The SAR showed that all cancer cell lines responded more favorably to the thien-2-yl group located at position 6 of pyrido[1,2-a]pyrimidine-3-carboxamide derivatives 6h–k, with an IC50 concentration of less than 10 µg/mL.

**STRUCTURE**

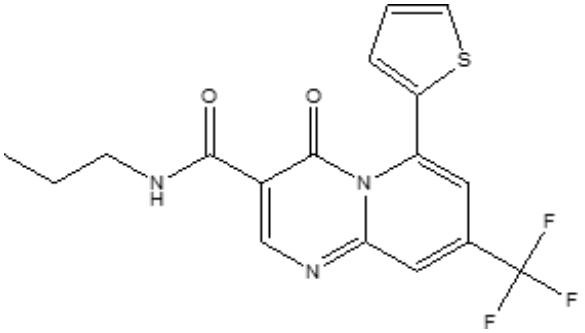
i) N-Methyl-4-oxo-6-(thiophen-2-yl)-8-(trifluoromethyl)-4H pyrido[1,2-a]pyrimidine-3-carboxamide (6h) :



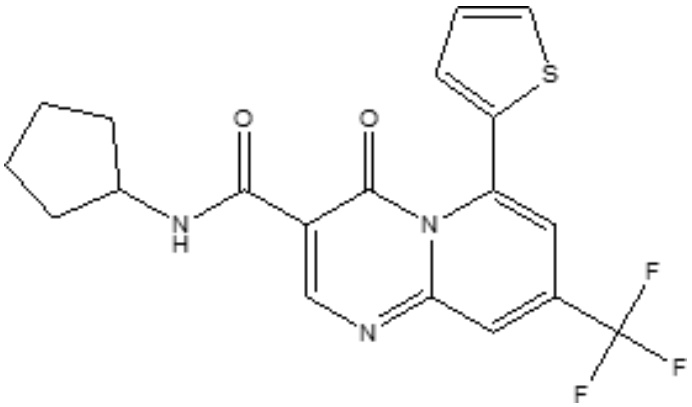

ii) N-Ethyl-4-oxo-6-(thiophen-2-yl)-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidine-3-carboxamide (6i):



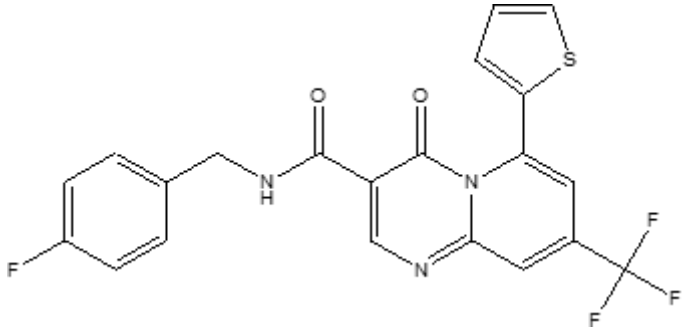

iii) 4-Oxo-N-propyl-6-(thiophen-2-yl)-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidine-3-carboxamide (6j):



iv) N-Cyclopentyl-4-oxo-6-(thiophen-2-yl)-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidine- 3-carboxamide (6k):



v) N-(4-Fluorobenzyl)-4-oxo-6-(thiophen-2-yl)-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidine-3-carboxamide (6n):

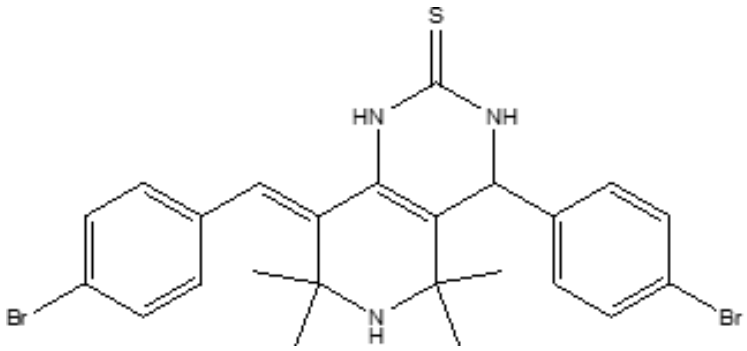


**Pyrido [4,3 - d] pyrimidine derivative research**

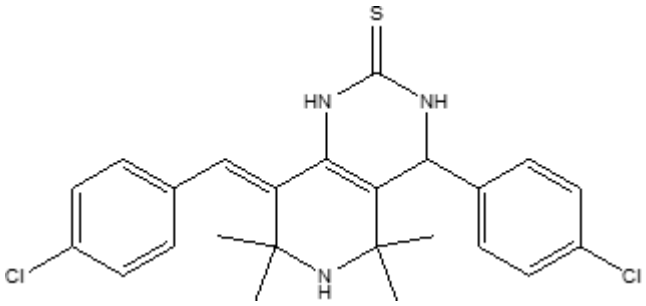
- Pyrido[4,3-d] pyrimidine derivatives with anticancer activity were synthesized and designed, as reported by Hanan A. Soliman et al. The antiproliferative activity of the synthetic compounds was assessed using the SRB assay against human lung cancer A549 cell lines, human hepatocellular carcinoma HepG2, and breast adenocarcinoma MCF-7 cell lines. Doxorubicin was used as the reference drug. It was discovered that compounds 11c and 11d exhibited greater anticancer efficacy than the standard drug (IC50: 4.40 and 4.75 respectively, compared to 4.80 µg/mL for doxorubicin). The Sulfo-Rhodamine-B stain (SRB) assay was used to quantify the antiproliferative activity in vitro.[ Ref. Synthesis of novel 1,6-naphthyridines, pyrano[3,2-c]pyridines and pyrido[4,3 d]pyrimidines derived from 2,2,6,6-tetramethylpiperidin-4-one for in vitro anticancer and antioxidant evaluation][31]

**Structure:**

i) 8-(4-Bromobenzylidene)-4-(4-bromophenyl)-5,5,7,7-tetramethyl-3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidine 2(1H)-thione (11d) :




ii) 8-(4-Chlorobenzylidene)-4-(4-chlorophenyl)-5,5,7,7-tetramethyl-3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidine 2(1H)-thione (11c):




**Pyrido [3,4 - d] pyrimidine research derivatives**

- In European Journal of Medicinal Chemistry & In journal of Bioorganic & Medicinal Chemistry H. Zhang et al reported synthesized 2,4,6-Trisubstitued pyrido[3,4-d]pyrimidine derivatives can serve as EGFR-TKIs. The most promising compound B30 inhibited HCC827 and H1975 cells growth with the IC50 values of 0.044 µM and 0.40 µM, respectively. The antiproliferative effects of synthesized compounds were evaluated against three human lung cancer cell lines including HCC827 (EGFRDel E746-A750), H1975 (L858R/T790M) and A549 (EGFR WT) by applying the MTT colorimetric assay. The third generation EGFR-TKI osimertinib was used as the positive control. compounds B1 and B2 displayed significant antiproliferative activity against HCC827 cells with IC50 values of 1.16 µM and 1.35 µM, respectively as it replaced benzene ring with pyridine.[32]

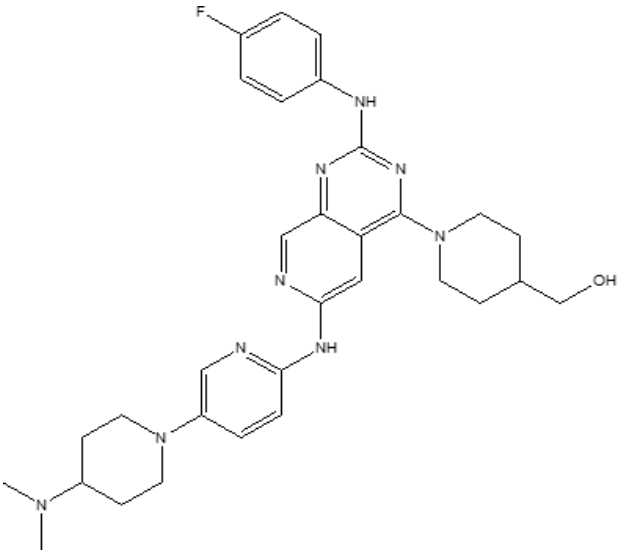
- The 4-(di ethylamino)piperidin-1-yl moity was found to be an appropriate substituted group at the pyridine ring's 5' position by SAR data. Compound B7, or trifluoromethyl, was added, and this caused a considerable reduction in the drug's ability to inhibit

HCC827 cells. A rigid benzene ring was preferable to a flexible ring at the pyrido[3,4-d]pyrimidine 2-position. To increase the antiproliferative effect, the hydroxyl group may interact with the phosphate binding site (PBS) of EGFR through additional hydrogen bond formation.

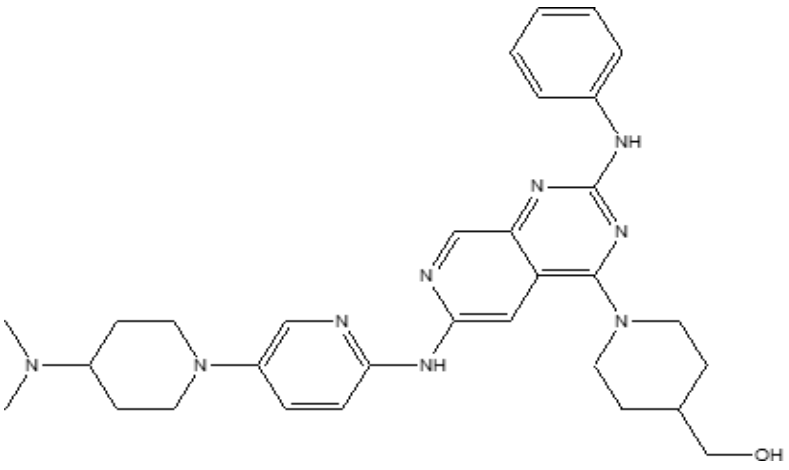
- The discussion of cell-based structures activity relationship suggested that phenylamino at 2-position, 4-hydroxymenthylcyclohexyl at 4-position and 5-(4-(dimethylamino)piperidin- 1-yl)-pyridin-2-yl at 6-position of pyrido[3,4-d] pyrimidine scaffold were beneficial for antiproliferative effects in designed compound.

**Structure**

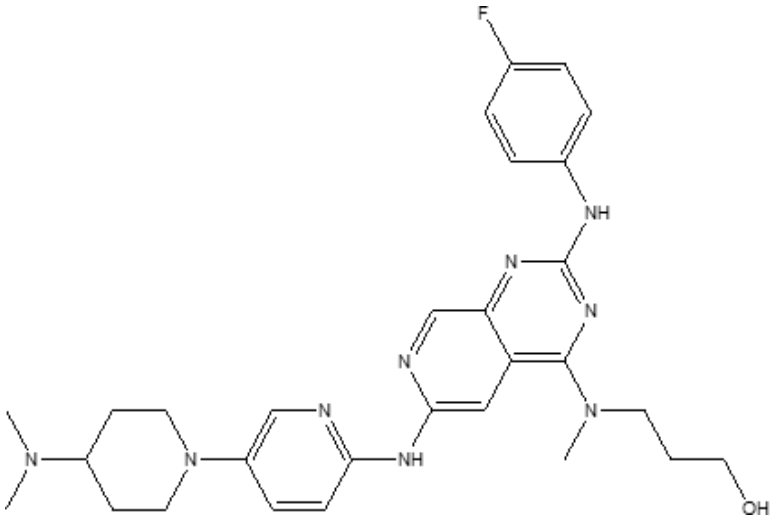
i) (1-(6-((5-(4-(Dimethylamino)piperidin-1-yl)pyridin-2-yl)amino)-2-((4-fluorophenyl)amino)pyrido[3,4-d]pyrimidin-4-yl)piperidin-4-yl)methanol (B30)




ii) (1-(6-((5-(4-(Dimethylamino)piperidin-1-yl)pyridin-2-yl)amino)-2-(phenylamino)pyrido[3,4-d]pyrimidin-4-yl)piperidin-4-yl)methanol (B29)

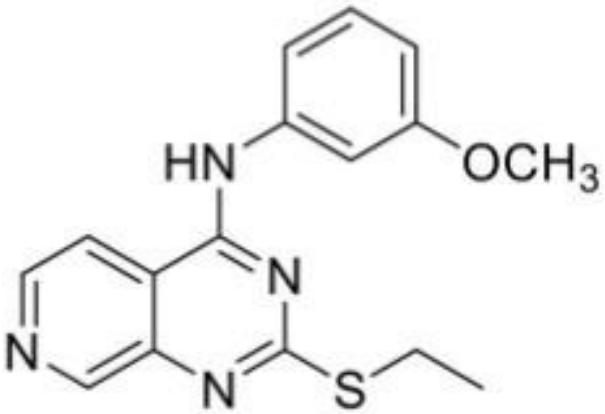


iii) 3-((6-((5-(4-(Dimethylamino)piperidin-1-yl)pyridin-2-yl)amino)-2-((4-fluorophenyl)amino)pyrido[3,4-d]pyrimidin-4-yl)(methyl)amino)propan-1-ol (B31)




- Novel pyrido[3, 4-d]pyrimidine derivatives' anti-tumor activity studies were reported by Wen-Ge Guo et al. 29 pyrido[3,4-d]pyrimidine compounds were designed, synthesized, and assessed in vitro using the MTT assay in order to identify anti-tumor medications with high efficacy and low toxicity. Compound 30 exhibited the best antitumor activity on MGC803 cells (IC50 = 0.59 μM), while the majority of the compounds had good antitumor activities, according to the results.[33]

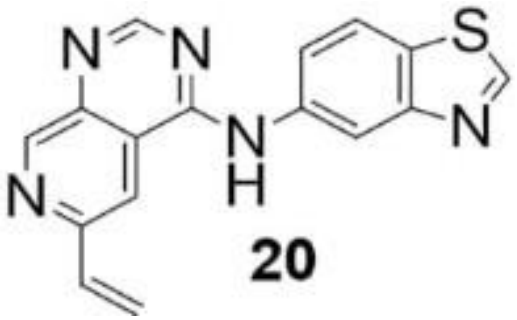
**Structure of compound 30**




- Pyrido[3,4-d]pyrimidine derivatives were synthesized to find new inhibitors of necroptosis, according to Namkyoung Kim et al. synthesized pyrido[3,4-d]pyrimidine derivatives as new inhibitors of necroptosis that can inhibit MLKL phosphorylation. Comparable to GSK872 (2), a representative selective RIPK3 inhibitor, compound 20 exhibits inhibitory activity against RIPK3-mediated pMLKL in HT-29 cells.

- According to the results of the biochemical kinase assay, 20 has activity against RIPK3 that is comparable to that of GSK872 (2) and is less potent against RIPK1 than GSK872, suggesting that 20 has a higher selectivity for RIPK3 over RIPK1 than GSK872. 20 prevents necroptosis in HT-29 cells by blocking MLKL oligomerization.[34]

**Structure of compound 20**




- According to Mengyan Ma. et al., compounds of pyrido[3,2-d]pyrimidine and pyrido[3,4-d]pyrimidine were created, produced, and tested for their biological activity against hematologic malignancies. At sub-nanomolar levels, compounds A1, A5, and A7 that contained pyrido[3,2-d]pyrimidine inhibited phosphoinositide 3-kinase-δ (PI3Kδ). In SU-DHL-6 cells, A7 triggered apoptosis and cell cycle arrest.[35]

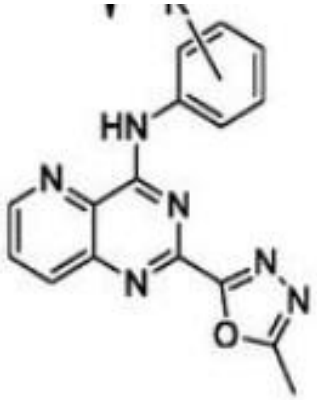
**Structure of compound A7**


**Pyrido[3,2-d]pyrimidines derivatives research**

- According to Arshiya Banu Syeda et al. Using the MTT procedure, a new group of structurally modified pyrido[3,2-d]pyrimidines (10a–j) with substituted aryl amino derivatives have been synthesized and tested for anticancer effects against the human prostate cancer cell line PC3, the lung cancer cell line A549, the breast cancer cell line MCF- 7, and the colon cancer cell line Colo-205.
- With IC50 values ranging from 0.013 ± 0.0058 µM to 8.22 ± 5.87 µM, the majority of the synthesized compounds demonstrated good to moderate anticancer activity. In contrast,

standard 9 etoposide, which is used as a standard drug, had IC50 values ranging from 0.14 ± 0.017 µM to 3.08 ± 0.135 µM, respectively. Compound 10e exhibited greater anticancer activity overall.[36]

**Structure of compound 10**




## CONCLUSION

➢ In conclusion, pyridopyrimidine derivatives have demonstrated remarkable potential as anticancer agents, exhibiting potent inhibitory activities against various cancer cell lines. From previous research the structural modifications and SAR studies have provided valuable insights into their biological activity, revealing opportunities for optimization. As research continues to unravel the complexities of cancer biology, pyridopyrimidine derivatives are poised to play a significant role in the development of novel anticancer therapies. This review provide current research states 0n pyridopyrimidine derivative that demonstrated the anticancer activity against different cancer cell line.

## Aim and objective

### Aim

The aim of this project is to provide comprehensive review of recentadvances in the development of pyridopyrimidine derivatives as potential anticancer agents and highlighting their structural activity relationship.

### Objective

1. To highlight the potential molecular targets of pyridopyrimidine derivatives.
2. To provide an overview of potential therapeutic applications of pyridopyrimidine derivatives.
3. To analyze the structural activity relationship (SARs) of pyridopyrimidinederivatives as anticancer agent.

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