RECENT ADVANCES ON PYRIMIDINE DERIVATIVES AS ANTICANCER AGENTS.

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Abstract

Cancer is a global health challenge; it impacts the quality of life and its treatment is associated with several side effects. Resistance of the cancer cells to the existing drugs has led to search for novel anticancer agents. Pyrimidine, a privileged scaffold, is part of living organisms and plays vital role in various biological procedures as well as in cancer pathogenesis. Due to resemblance in structure with the nucleotide base pair of DNA and RNA, it is recognized as valuable compound in the treatment of cancer.

Objectives

Many novel pyrimidine derivatives have been designed and developed for their anticancer activity in the last few years. The present review aims to focus on the structure of pyrimidine derivatives as anticancer agent from the last decade.

Results

In summary, the development of more potent and efficacious anticancer drugs with pyrimidine scaffold will continue to be a promising scaffold over the next 20 years.

Keywords: Pyrimidine, cancer, EGFR, VEGFR inhibitors

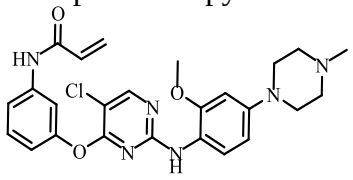
Introduction

In the past few decades, pyrimidines, an attractive class of heterocyclic compounds, have been known by the wide range of biological activities (Kumar and Narasimhan 2018). Pyrimidine containing derivatives have been emerged as a promising and attractive one in the development of potent antitumor agents with different molecular targets (Faraji, *et al*. 2021) depending on its substitution pattern.

1. Pyrimidine-containing compounds as selective EGFR TKIs

Different pyrimidine-based analogs have been integrated and assessed for their capacity to target different protein kinase catalysts, including EGFR tyrosine kinase. These sorts of inhibitors were effectively intended to target various changes in tyrosine kinase domain of EGFR and utilized as the compelling specialists against a few tumors with EGFR over-enactment like non-little cell cellular breakdown in the lungs (NSCLC) (Walter, *et al*. 2013). Clinical data have shown the significant influence of pyrimidine derivatives as EGFR TK inhibitors in several successful FDA-approved drugs (Ayati, *et al*. 2021, Zhong, *et al*. 2021).

WZ40028 ١ is the first reported pyrimidine-based compound to belong to the third generation EGFR-TK inhibitor with promising inhibitory activity against the mutant $EGFR^{T790M}$ (Chen, *et al*. 2017). Osimertinib ٢ (AZD9291) is the first FDA-approved pyrimidine-containing drug to show significant clinical efficacy against NSCLC (Girard 2019). In addition, olmutinib ٣ (HM61713) was developed as other example from the third-generation EGFR TK inhibitors with advantages of increased residence time to EGFR by alkylating Cys797 (Lu, *et al*. 2018). Moreover, studies are as yet progressing to find more proficient pyrimidine containing EGFR inhibitors.



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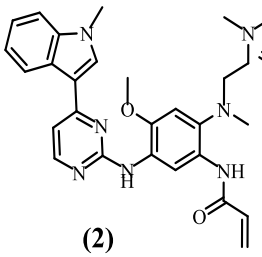

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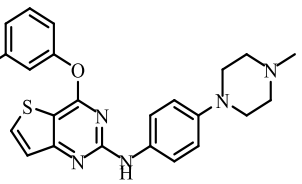

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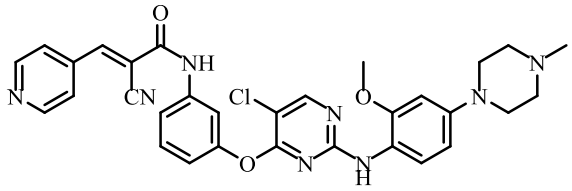
1.1. Amino pyrimidine derivatives:

1.1.1. 2-Amino-pyrimidine derivatives

Some 2-anilino-pyrimidine derivatives were designed and synthesized as covalent reversible WZ40028 analogs. Among the synthesized derivatives, 2-cyano-acrylamide scaffolds exhibited strong activity and selectivity against mutants $EGFR^{L858R}$and $EGFR^{L858R/T790M}$ with IC_{50} less than 2.5 μM. Compound **4** containing polar motif (4-pyridyl group) was found to be the most potent inhibitor with IC_{50} = 37 nM against double mutant EGFR $^{L858R/T790M}$ (Basu, *et al*. 2015).



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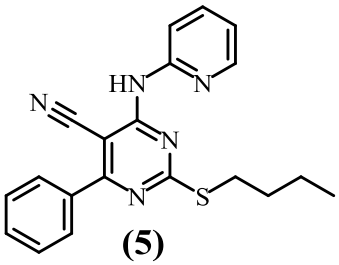
1.1.2. 4-Amino-pyrimidine-5-carbonitrile derivatives

Another series of pyrimidine-5-carbonitrile subordinates has been planned as ATP emulating tyrosine kinase These mixtures were orchestrated and considered for their *in vitro* cytotoxic activities in contrast to HCT-116, HepG2, MCF-7, and A549 cell lines. Compound **5** showed 4.5- to 8.4-folds of erlotinib activity against HCT-116, HepG-2, MCF-7, and A549 cells with IC_{50} values of 3.37, 3.04, 4.14, and 2.4 µM, respectively. In addition, compound **15** was also found to be the most active compound against both $EGFR^{WT}$ and mutant $EGFR^{T790M}$, exhibiting IC_{50} values of 0.09 and 4.03 µM, respectively (Nasser, *et al*. 2020).



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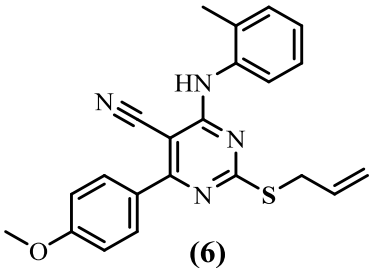
Ibrahim *et al* (Osman, *et al.* 2022) reported the design and synthesis of pyrimidine-5-carbonitrile based derivatives as EGFR inhibitors with anticancer and apoptotic activity. The target pyrimidines were evaluated *in vitro* for their anticancer activity against HepG2, A549 and MCF-7 cell lines. Compound **6** exhibited excellent activity against HepG2, A549 and MCF-7 with IC_{50} values of 3.56, 5.85 and 7.68 µM, respectively, compared to erlotinib. Moreover, compound **6** was emerged as the most potent EGFR inhibitor with an IC_{50} value of 8.29 nM, in comparing with that of erlotinib (IC_{50} = 2.83 nM).



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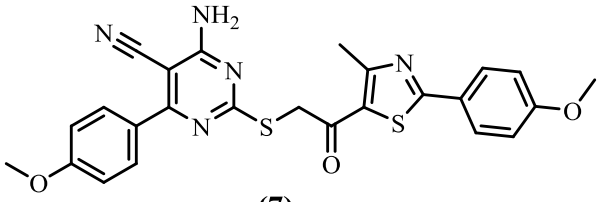
(Sahin, *etal*, 2021) discovered a series of 4-aminopyrimidine-5-carbonitrile analoges as effective agents against for glioblastoma tumors. Compound **7** showed an anti-proliferative IC_{50} of 1.56 mM, which is slightly higher activity than cisplatin (1.67 mM).



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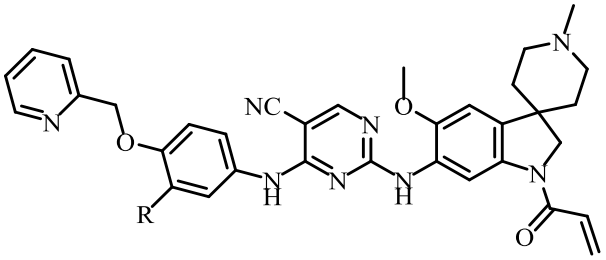
1.1.3. 2,4-Diamino-substituted pyrimidine derivatives

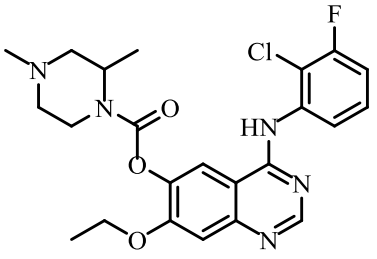
A series of 2,4-diamino-pyrimidine containing spiro structures were prepared and evaluated as dual EGFR and HER2 inhibitors under 0.5 M drug concentration. Compounds **8a,b** showed the highest inhibitory effects against a panel of EGFR kinases especially against both mutants T790M and L858R EGFR kinases which were 31 times more stronger than neratinib as standard drug (IC_{50} ranging from 0.05 to 0.2 μM) (Ye, *et al.* 2019).



(8a) **R = H**
(8b) **R = Cl**

1.1.4. 4,6-Diamino-substituted pyrimidine derivatives

A series of 4,6-disubstituted pyrimidines derivatives were synthesized and evaluated as EGFR inhibitors for patients with NSCLC (Zhang, *et al.* 2018). Rational of this research was depended on the use of 4,6-disubstituted pyrimidine as core structure to replace the quinazoline basic skeleton of the lead structure, AZD3759 **9** via an approach involving scaffold hopping. It was found that compound **10** exhibited the best inhibitory effect compared with AZD3759 *in vitro* and *in vivo*.



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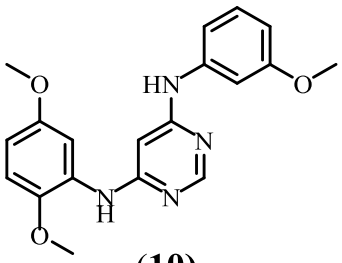

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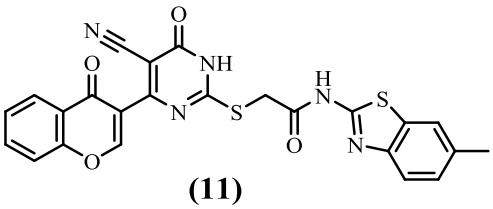
1.1.5. Miscellaneous derivatives

Abdellatif *et al*. synthesized a number of pyrimidine-benzothiazole hybrid derivatives as new multi-targeted anticancer agents. Compounds **11** and **12** showed better inhibitory potency and selectivity towards EGFR and HER2 enzymes (IC_{50} less than 1 μM) compared to lapatinib and 5-FU as standards (Abdellatif, *et al*. 2020).



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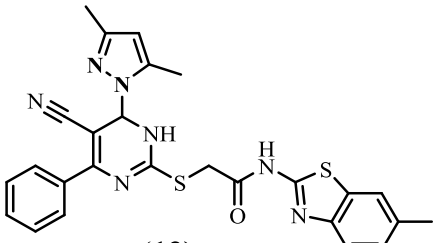

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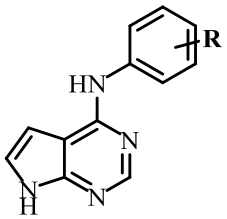
1.2. Heterocyclic-fused pyrimidine derivatives

1.2.1. Pyrrolo-pyrimidine derivatives

A number of compounds containing pyrrolo[2,3-*d*]pyrimidine scaffold were synthesized and evaluated for their inhibitory effects against EGFR kinases. All the target compounds exhibited promising effects. Compounds **13a,b** bearing 3-bromophenyl and 3-bromo-4-chlorophenyl derivatives demonstrated the highest EGFR inhibitory activity with IC_{50} of 3.76 and 3.63 nM, respectively (Kurup, *et al.* 2018).

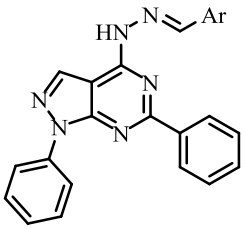


(13a) R = 3-Br

(13b) R = 3-Br, 4-Cl

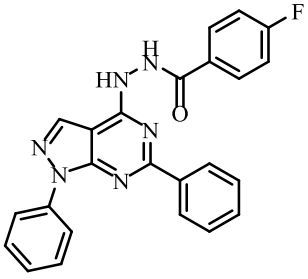
1.2.2. Pyrazolo-pyrimidine containing compounds

Two series of 1*H*-pyrazolo[3,4-*d*]pyrimidine derivatives were designed, synthesized and evaluated *in vitro* for their inhibitory activities against $EGFR^{WT}$. Compounds **14a,b** and **15** potently inhibited $EGFR^{WT}$ at sub-micro molar IC_{50} values comparable to that of the reference erlotinib. Furthermore, compound **15** was a good apoptotic agent, which arrested HepG2 cell cycle at G0/G1 and G2/M phases (Gaber, *et al.* 2018).



(14a) Ar = 4-NO_2-C_6H_4

(14b) Ar = 1-Naphthyl



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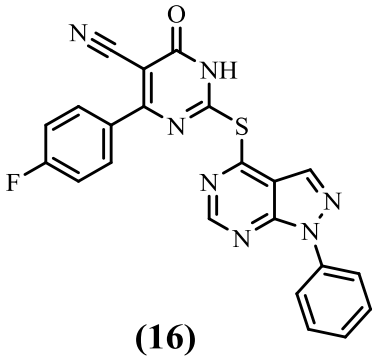
A series of some 4-substituted-1-phenyl-1*H*-pyrazolo- [3,4-*d*]pyrimidine derivatives were designed EGFR-TK inhibitors and screened for their antitumor activity against breast (MCF-7) and lung (A549) cell lines. Compound **16** elicited the highest EGFR-TK inhibitory activity (91%) (Abbas, *et al*. 2015).



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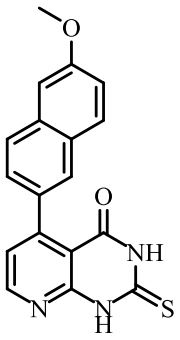
1.2.3. Pyrido-pyrimidine based compounds

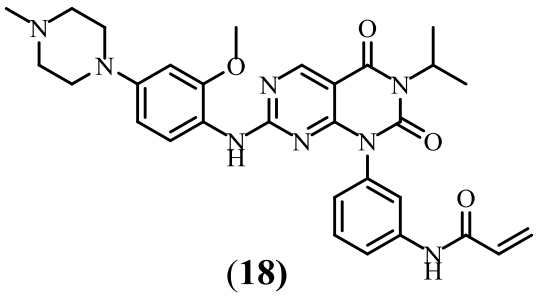
El Sayed *et al.* synthesize pyrido[2,3-*d*]pyramidines as small molecules that can inhibit tyrosine kinase in cancer cells . The best results were seen by compound **17** with 81.7% inhibition at 25 nM concentration in an enzymatic kinase assay and IC_{50} = 8.4 nM against MCF-7 cells in cell-based assay which was comparable to sorafenib as the reference drug (IC_{50} = 7.66 nM). This compound also showed promising antitumor activity against leukemia and renal cancer cell lines (El Sayed, *et al.* 2018).



(**17**)

1.2.4. Pyrimido-pyrimidine derivatives

A series of pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives was designed and synthesized as novel potent and selective $EGFR^{L858R/T790M}$ inhibitors. The most promising compound **18** showed a favorable selectivity at both *in vitro* and *in vivo* levels, indicating that compound **18** might be used as a promising drug candidate to overcome $EGFR^{L858R/T790M}$ drug-resistance mutation (Hao, *et al*. 2018).



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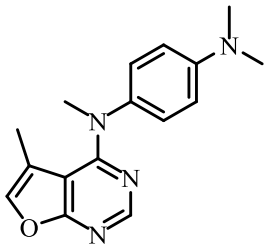
1.2.5. Furo-pyrimidine based compounds

A number of EGFR kinase inhibitors containing 4-substituted-5-methyl-furo[2,3-*d*]pyrimidine core structure have been developed. Compound **19** showed the highest EGFR kinase inhibition in enzymatic assay with IC_{50} = 3.1 nM and potent anti-proliferative activity toward A431 cells in cell-based assay (IC_{50} = 1 nM) (Devambatla, *et al*. 2018).



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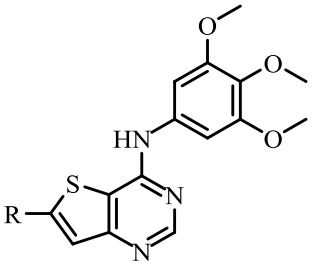
1.2.6. Thieno-pyrimidine derivatives

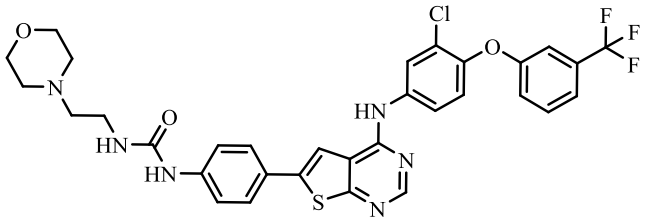
A series of 4-trimethoxyanilinothieno[3,2-*d*]-pyrimidine derivatives were discovered as novel dual EGFR kinase and microtubule polymerization inhibitors. The most representative compound **20a** manifested potent anti-proliferative activity toward all tested cell lines (A549, HeLa, HT29, Jurkat, RS4; 11) with IC_{50} values ranging from 0.001 to 0.02 μM. In addition, compound **20a** inhibited tubulin assembly and EGFR activity with an IC_{50} values of 0.71 μM, and 30 nM, respectively. While, compound **20b** showed the highest inhibitory effect against EGFR kinase (IC_{50} = 2.5 nM) compared with erlotinib as the standard drug (IC_{50} = 1.5 nM) (Romagnoli, *et al*. 2019).



(20a) **R = 4-CH_3-C_6H_4**

(20b) **R = 2-Thienyl**

Milik and co-workers developed a series of thieno[2,3-d]pyrimidine-based dual EGFR/HER2 inhibitors with the aim of overcoming the resistance against EGFR inhibitors. Compound **21** was identified as a dual EGFR/HER2 inhibitor with IC_{50} values of 91.7 nM and 1.2 μM, respectively (Milik, *et al*. 2018).



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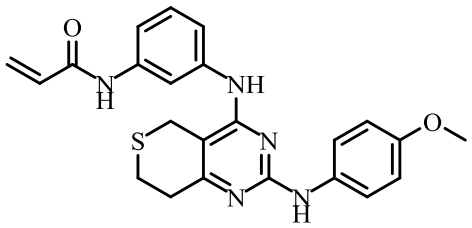
1.2.7. Thiopyrano-pyrimidine derivatives

A series of thiapyran-pyrimidine derivatives were synthesized as novel olmutinib derivative and evaluated their antiproliferative. The most promising compound **22** exhibited the similar IC_{50} values on A549 and H1975 cell lines to the lead drug olmutinib, and exhibited excellent activity and selectivity on $EGFR^{T790M/L858R}$ in the kinase experiment (Xiao, *et al*. 2020).



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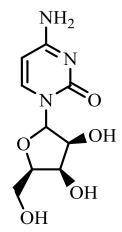
2. Pyrimidine-containing compounds as pyrimidine antagonists, (DNA polymerases, and ribonucleotide reductase inhibitors)

Pyrimidines such as cytosine are incorporated into DNA as deoxycytidine triphosphate (dCTP), and competitive inhibition of this incorporation by Arabinofuranosylcytosine triphosphate (Ara-CTP) causes deregulation and inhibition of a wide range of enzymes including DNA polymerase and ribonucleotide reductase (Townsend and Cheng 1987, Baker, *et al*. 1991). Both enzymes catalyze the synthesis of DNA in every living cell using the four deoxyribonucleotide building blocks dATP, dGTP, dCTP, and dTTP. Pyrimidine antagonists, as cytarabine **23** (Patrick 2013) and gemcitabine **24** (Toschi, *et al*. 2005) are widely used in chemotherapy regimens as DNA polymerases and ribonucleotide reductase inhibitors, respectively for colorectal, breast, head and neck, non-small-cell lung cancer, pancreatic cancer and leukemia's (Maring, *et al*. 2005).



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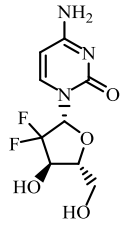

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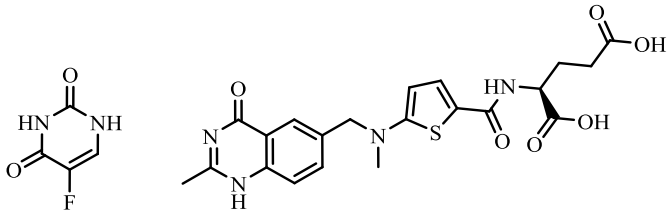
3. Pyrimidine-containing compounds as thymidylate synthase inhibitors.

Thymidylate synthase (TS) is essential for the production of deoxythymidine triphosphate (dTTP) which involved in DNA synthesis. 5-Fluorouracil (5-FU) **25** and

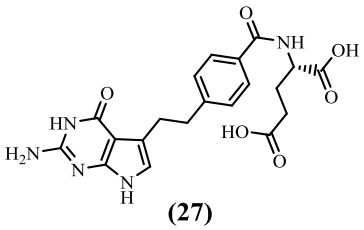
raltitrexed **26**, are pyrimidine analogs that inhibit the TS in the folate synthesis pathway (Adjei 2000, Baguley and Kerr 2001).



(25) **(26)**

4. Pyrimidine-containing compounds as dihydrofolate reductase inhibitors.

Pemetrexed **27** is a multi-targeted antifolate that has demonstrated antitumor activity in various tumor types as a single agent and in combination with other chemotherapeutic agents. Pemetrexed is the first agent approved for the treatment of malignant pleural mesothelioma (MPM). In August 2004, pemetrexed was approved as a second-line, single-agent treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) (Rollins and Lindley 2005).



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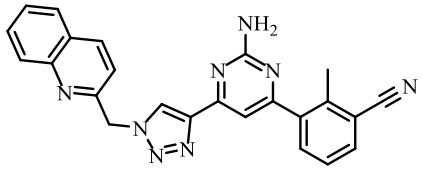
5. Pyrimidine-containing compounds as adenosine receptor antagonists

A series of dual A_{2A}/A_{2B} adenosine receptor (AR) antagonists based on the triazole-pyrimidine-methylbenzonitrile core were designed and synthesized. Compound **28** displayed better inhibitory activity on A_{2B} AR (IC_{50} = 14.12 nM) (Li, *et al*. 2022).



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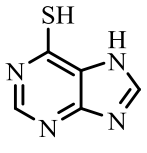
6. Pyrimidine-containing compounds as purine antagonists

Purine is a heterocyclic aromatic organic compound that consists of two rings (pyrimidine and imidazole) fused together. Purines are integral components of RNA, DNA and coenzymes that are synthesized in proliferation of cancer cells. Therefore, an agent that antagonizes the purine will certainly lead to formation of false DNA. 6-Mercaptopurine (6-MP) **29** and azathiopurine **30** are belonging to this class (Patrick 2013).



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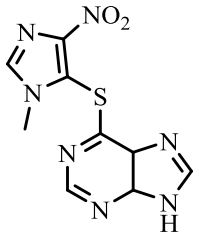

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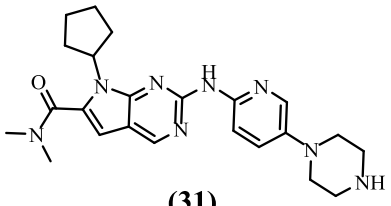
7. Pyrimidine-containing compounds as cyclin-dependent kinase (CDK) 4 and 6 inhibitors

In 2017, ribociclib **31** and abemaciclib **32** are an orally available, small molecules have been approved by US FDA for the treatment of HR +/HER2- advanced or metastatic breast cancer in postmenopausal women, in combination with an aromatase inhibitor (letrozole) or with a selective estrogen receptor degrader (fulvestrant), respectively (Vidula and Rugo 2016, Syed 2017, Royce, *et al.* 2022). Both ribociclib and abemaciclib are pyrimidine core and classified as cyclin-dependent kinase (CDK) 4 and 6 inhibitors (Gupta, Narayanan et al. 2019, Food and Administration 2021).

In 2020, the Food and Drug Administration approved brigatinib **33** (Alunbrig®) for adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.



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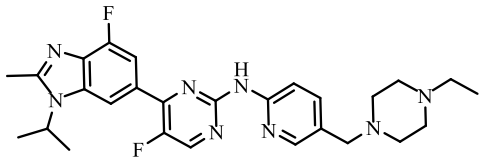

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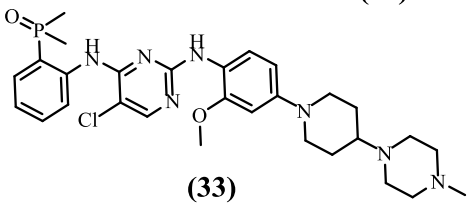
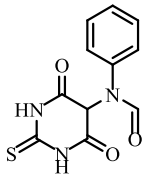


(33)

8. Pyrimidine-containing compounds as topoisomerase II inhibitors

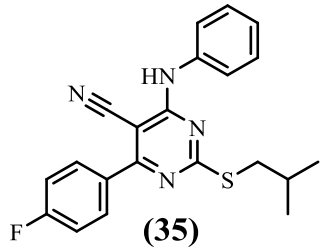
Merbarone® **34** is a catalytic inhibitor of topoisomerase II. The compound underwent Phase I and Phase II Clinical Trials primarily in the late 1980s and 1990s. Merbarone®, showed antitumor activity against the murine L1210 leukemia and important activity against some other murine tumors (Larsen, *et al*. 2003).



(34)

9. Pyrimidine-containing compounds as COX-2 selective inhibitors

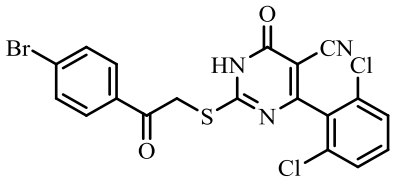
Some cyanopyrimidine derivatives were synthesized and evaluated as COX-2 selective inhibitor anticancer agents (Akhtar, *et al*. 2020). Compound **35** exhibited superior anticancer activity against ovarian cancer with GI_{50}-value of 0.33 μM and selectivity index of 4.84 in comparison to 5-fluoro uracil (5-FU) which exhibited GI_{50}-value 4.43 μM. In addition, showed that compound **35** displaying broad anticancer activity were more selective towards COX-2 as compared to COX-1.



(35)

10. 6-Aryl-5-cyano thiouracils as potential anticancer agents.

Several 6-aryl-5-cyanothiouracil derivatives were synthesized and explored for their anticancer activities. The preliminary screening results showed that, compounds **36** and **37** displayed potent growth inhibitory effects toward non-small cell lung cancer (HOP-92) and leukemia (MOLT-4) cell lines, respectively (Taher and Abou-Seri 2012).



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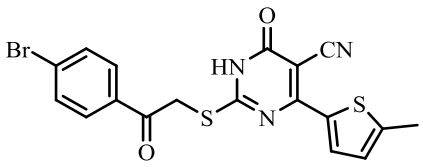
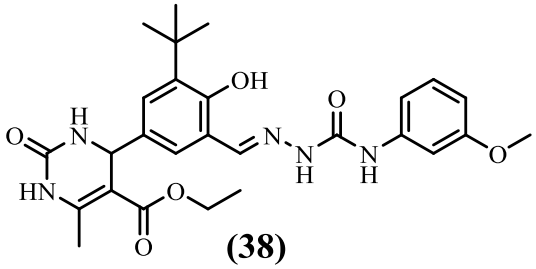


(37)

11. Dihydropyrimidinones as potential anticancer agents.

A series of dihydropyrimidinone-semicarbazone hybrids as potential human DNA ligase 1 inhibitors have been synthesized. Compound **38** showed selective antiproliferative activity against HepG2 cells in a dose-dependent manner with an IC_{50} value of 10.07 μM (Sashidhara, *et al*. 2016).

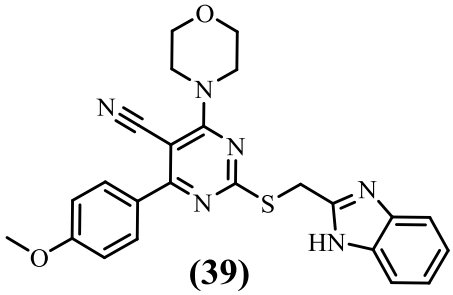


(38)

12. Cyanopyrimidine derivatives as anticancer agents.

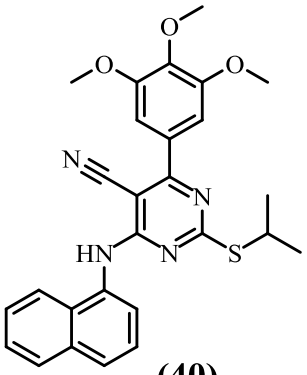
Several analogs of benzimidazole pendant cyanopyrimidine derivatives were

synthesized and evaluated for their *in-vitro* anticancer activities at National Cancer Institute (NCI) USA, against NCI-60 cancer cell lines. Compound **39** was found to be the most active amongst the synthesized compounds (Haoran, *et al.* 2020).



(39)

A series of 3,4,5-trimethoxy phenyl ring pendant sulfur-containing cyanopyrimidine derivatives were *in vitro* piloted against a panel of 60- NCI cancer cell lines. Compound **40** displayed the most promising broad-spectrum anticancer activity with high growth inhibition of various cell lines representing multiple cancers diseases. Mechanistic investigation of compound **40** in human breast cancer MDA-MB-231 cells showed that compound 4e triggers cell death through the induction of apoptosis (Nainwal, *et al*. 2020)



(40)

Conclusion

Kinases are crucial mediators of signal transduction processes, and by catalyzing the transfer of phosphates from high-energy donor molecules, such as ATP to other specific substrates, so they are key regulators of a variety of cell functions. One of the largest groups of kinases is protein kinases, which act on and modify the activity of specific proteins. Kinases play a crucial role for kinases in the carcinogenesis and metastases of various types of cancer. However, dysregulation of kinases has been demonstrated in many human disorders including cancer. Therefore, inhibition of PKs has been shown to be a promising therapeutic strategy for treatment of various tumors. We discuss how the challenge of drug resistance to kinase inhibitors is being met and the future of kinase drug discovery.

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التطورات الحديثة على مشتقات البيرميدين كعوامل مضادة للسرطان.

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السرطان هو أحد التحديات الصحية العالمية. يؤثر على نوعية الحياة ويرتبط علاجها بالعديد من الآثار الجانبية. أدت مقاومة الخلايا السرطانية للأدوية الموجودة إلى البحث عن عوامل جديدة مضادة للسرطان. البيريميدين ، نواه مميزة ، هي جزء من الكائنات الحية وتلعب دورًا حيويًا في الإجراءات البيولوجية المختلفة وكذلك في التسبب في الإصابة بالسرطان. نظرًا للتشابه في التركيب مع زوج قاعدة النيوكليوتيدات من الحمض النووي والحمض النووي الريبي ، فقد تم التعرف عليه كمركب قيم في علاج السرطان.

الاهداف :
تم تصميم العديد من مشتقات البيريميدين الجديدة وتطويرها من أجل نشاطها المضاد للسرطان في السنوات القليلة الماضية. تهدف المراجعة الحالية إلى التركيز على بنية مشتقات البيريميدين كعامل مضاد للسرطان من العقد الماضي.

النتائج : باختصار ، سيظل تطوير عقاقير أكثر فعالية وفعالية مضادة للسرطان باستخدام هيكل بيريميدين بمثابة نواه واعدة على مدار العشرين عامًا القادمة.

الكلمات المفتاحية : البيريميدين, السرطان, مثبطات مستقبل عامل نمو البشرة و عامل النمو الوعائى البطانى