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Recent Studies on the Anticancer Activity of Pyrimidine Derivatives: A Review

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ABSTRACT:

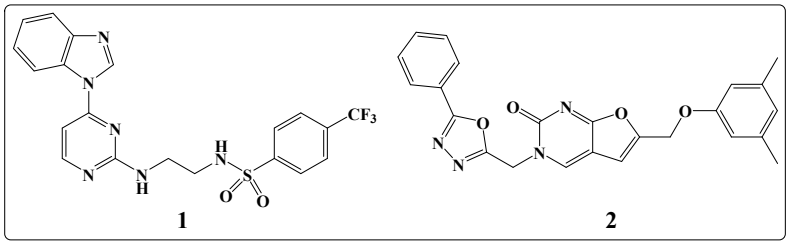
Pyrimidine and their derivatives are of great interest because they exhibit a wide spectrum of biological activities. It is one of the building blocks of the nucleic acids DNA and RNA. Various analogues of pyrimidine exhibit a wide range of and potent activities, such as antibacterial, antifungal, anti-inflammatory, analgesic, antihypertensive, antiviral, antidiabetic, anticonvulsant, antioxidant, and anticancer activities. The purpose of this review is to emphasize recent studies carried on the anticancer activities of pyrimidine derivatives.

Keywords: Anticancer, Antitumor, Antiproliferative, Inhibitors, Pyrimidine,

Introduction

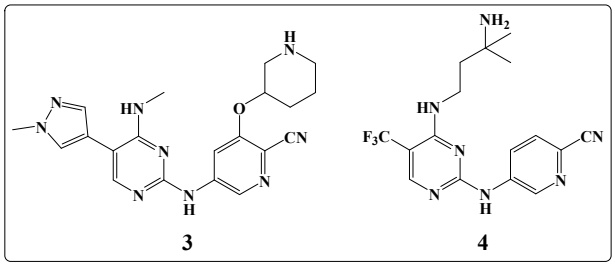
Cancer is considered a major public health problem, being one of the leading causes of death worldwide. According to GLOBOCAN 2020, there were 19.3 million new cancer cases worldwide in 2020, of which nearly 10 million people died from cancer. Lung, colon, prostate, and stomach cancers, as well as breast cancer in women, were the most common cancers [2]. Drug resistance, immune system and metastasis of cancer cells greatly limit prognosis and treatment, making the development of suitable anti-cancer drugs a major challenge for scientists [3, 4].

Pyrimidine and their derivatives are of great interest because they exhibit a wide spectrum of biological activities. It is one of the building blocks of the nucleic acids DNA and RNA. Various analogues of pyrimidine exhibit a wide range of and potent activities, such as antibacterial [5], antifungal [6], anti-inflammatory [7], analgesic [8], antihypertensive [9], antiviral [10], antidiabetic [11], anticonvulsant [12], antioxidant [13], and anticancer activities [14]. This review emphasizes recent studies on the anticancer activities of pyrimidine derivatives.



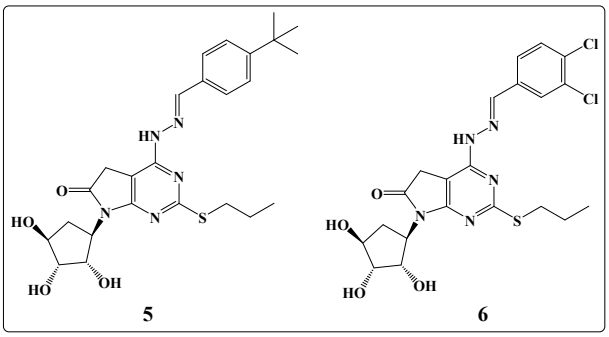
1 **2**

Following the structure of well-established V600EBRAF inhibitors, *Abdel-Maqsood et al* synthesized a novel series of 4-(1H-benzo[d]imidazol-1-yl)pyrimidin-2-amine linked sulfonamide derivatives and tested them for their strongest inhibitory activity against V600EBRAF at fixed concentrations.[15] Compound **(1)** showed the most significant growth inhibition against NCI 60 cancer cell lines. *El Mansouri et al* have synthesized a new series of furo[2,3-d]pyrimidine-1,3,4-oxadiazole hybrid derivatives using the Songoashira-heterocyclization protocol and evaluated their cytotoxic activities in four human cancer cell lines: fibrosarcoma (HT-1080), breast (MCF-7 and MDA-MB-231), and lung carcinoma (A549).[16] Compound **(2)** exhibits moderate cytotoxicity, with IC_{50} values ranging from 13.89 to 19.43 μM. Furthermore, compound 8f induces apoptosis through caspase 3/7 activation, mitochondrial pathway-independent cell death, and cell cycle arrest in S phase for HT1080 cells and G1/M phase for A549 cells.



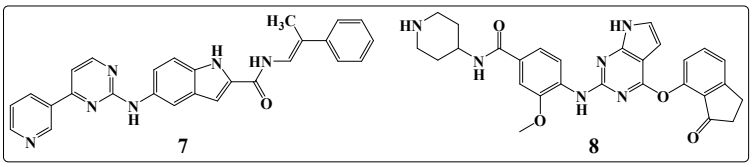
3 **4**

Jin et al used a strategy of trifluoromethyl substitution to obtain an orally bioavailable CHK1 inhibitor to overcome the limitations of the lead compound **(3)**, which can only be administered intravenously.[17] The investigation showed that compound **(4)** showed high plasma exposure in mice and also showed good kinase selectivity. Furthermore, it exhibited a significant antiproliferative effect in MV-4-11 cells and a synergistic effect in combination with gemcitabine in HT-29, A549 and RPMI-8226 cells. In addition, compound **(4)** could inhibit tumor growth in the MV-4-11 xenograft mouse model.



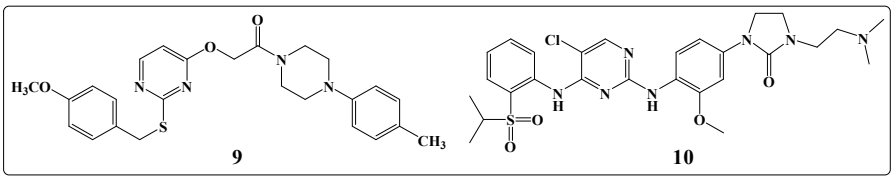
5 **6**

To obtain new anticancer agents with antimetastatic adjuvant efficacy, *Zhao et al* synthesized a series of novel N4-hydrazone derivatives of 5,7-dihydro-6H-pyrrolo[2,3-d]pyrimidin-6-one and evaluated them for their antiproliferative activity against A549 and MCF-7 cells.[18] Compounds **(5)** and **(6)** not only showed potent antiproliferative activity against A549 (IC_{50} = 15.3 and 21.4 μM) and MCF-7 (IC_{50} = 15.6 and 10.9 μM) cell lines, but also showed some anti-platelet aggregation activity.



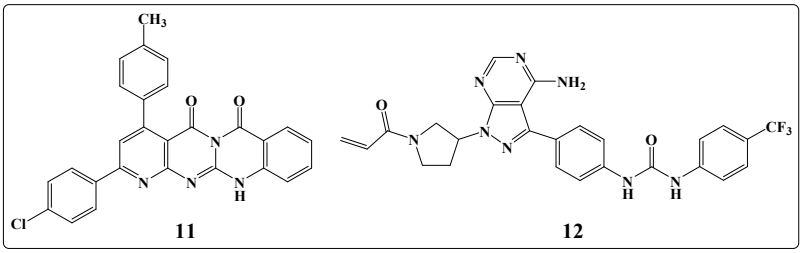
7 **8**

Wu et al described the synthesis and vacuole-inducing activity of 5-(4-(pyridin-3-yl)pyrimidin-2-yl)amino)-1H-indole-2-carbohydrazide derivatives that exhibited excellent vacuole-inducing activity. Notably, compound **(7)** effectively induced methotrexate in the tested cancer cells but not in human normal cells. Furthermore, **(7)** showed significant inhibition of tumor growth in the MDA-MB-231 xenograft mouse model. The excellent potency and selectivity of **(7)** motivates the development of methotrexate inducers. *Wei et al* described the discovery of focal adhesion kinase (FAK) inhibitors using a scaffold hopping strategy. Compound **(8)** exhibited potent inhibitory activity against FAK inhibitors, not only reducing the migration and invasion of PA-1 cells but also reducing the expression of MMP-2 and MMP-9. Furthermore, **(8)** inhibited tumor growth and metastasis, and no obvious adverse effects were observed.



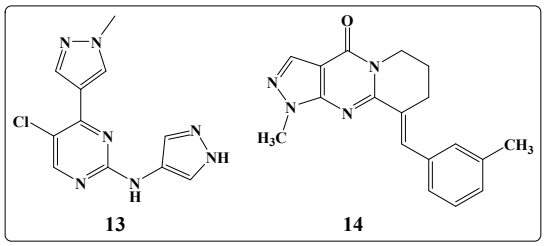
9 **10**

Deveshegowda et al have synthesized several uracil amides cleave poly (ADP-ribose) polymerase and novel thiouracil amide compounds and screened them for cell viability destruction in human-estrogen-receptor-positive breast cancer cell lines.[21] Compound **(9)** exhibited significant efficacy against human breast cancer cells with an IC_{50} value of 18 μM. Further compounds **(9)** increased the catalytic activity of PARP1, enhanced cleavage of PARP1, enhanced phosphorylation of H2AX, and increased CASPASE 3/7 activity. *Chang et al* found that the compound **(10)**, a novel ceritinib derivative, can inhibit the proliferation of ALK-positive ALCL cells, induce apoptosis of Karpas299 cells through the mitochondrial pathway in a caspase-dependent manner.[22] In addition, compound **(10)** can suppress ALK and downstream pathways including PI3K/Akt, Erk and JAK3/STAT3, and reduce the nuclear translocation of NFκB by inhibiting the TRAF2/IKK/IκB pathway. Taken together, the findings suggest that compound **(10)** shows more effective activity than ceritinib against ALK-positive ALCL.



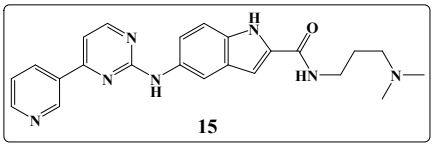
11 **12**

In search of essential pharmacophoric features of EGFR inhibitors, *Elzahbi et al* designed and synthesized a new series of pyrido[2,3-d]pyrimidine-4(3H)-one derivatives.[23] Compound **(11)** showed the highest inhibitory activity against EGFRWT and EGFRT790M with IC_{50} values of 0.099 and 0.123 μM, respectively. In addition, it induced cell cycle arrest at the pre-G1 phase and a significant apoptotic effect in PC-3 cells. Furthermore, compound **(11)** increased the level of caspase-3 by 5.3-fold in PC-3 cells. *Wu et al* reported the discovery of pyrrolo[2,3-d]pyrimidin/pyrazolo[3,4-d]pyrimidin-4-amine derivatives as a new class of FGFRs-dominant multi-target receptor tyrosine kinase inhibitors.[24] Compounds **(12)** showed excellent inhibitory activity against a variety of receptor tyrosine kinases and exhibited excellent potency in the SNU-16 gastric cancer cell line. The compound **(12)** induces FGFR1 phosphorylation and downstream signaling pathways as well as cell apoptosis.



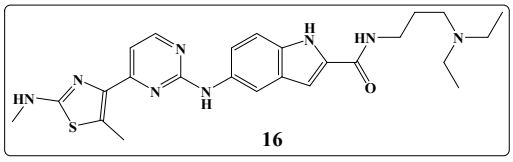
13 **14**

Cyclin-dependent kinase 2 (CDK2) is gaining significant interest as a target for developing new cancer therapies and for overcoming resistance to CDK4/6 inhibitors. *Fanta et al* reported a novel series of N,4-di(1H-pyrazol-4-yl) pyrimidin-2-amines that exhibited CDK2 inhibitory activity.[25] Among them, compound **(13)** were the most potent CDK2 inhibitors (Ki = 0.005 μM) with a degree of selectivity. The compounds exhibited sub-micromolar antiproliferative activity against a panel of 13 cancer cell lines. *Ruzzi et al* investigated the anti-cancer properties of the novel compound **(14)** and demonstrated excellent anti-proliferative activity against sixteen human cancer cell lines.[26] The effect of **(14)** on cell proliferation was found to be more prominent in high expressing cells than in low expressing cells. Compound **(14)** also exhibits excellent anti-cancer potential towards the HGC-27 gastric cancer cell line.



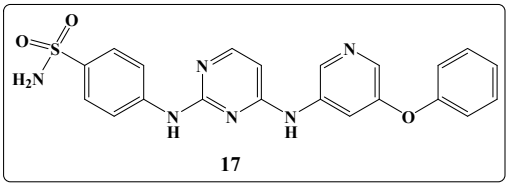
15

A series of 5-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)-1H-indole-2-carboxamide derivatives were designed, synthesized and evaluated as potent Nur77 modulators by *Qin et al*.[27] Among the synthesized compounds, **(15)** showed good potency against different liver cancer cell lines and exhibited lower toxicity than the positive compound celastrol. Also, compound **(15)** exhibited excellent Nur77-binding activity compared with the reference compound celastrol. Notably, compound **(15)** has good anti-hepatocellular carcinoma (HCC) activity.



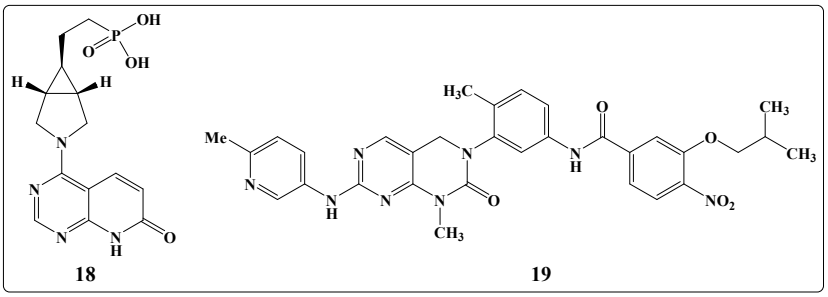
16

Further, *Qin et al* have synthesized some novel 5-(pyrimidin-2-ylamino)-1H-indole-2-carboxamide derivatives for potential anti-breast cancer activities.[28] Among these, compound **(16)** exhibited improved Nur77-binding ability (KDSPR(Nur77) = 91 nM) and excellent anti-proliferative activity against breast cancer cell lines. In addition, compound **(16)** significantly suppressed the growth of MDA-MB-231 xenograft tumors but had no obvious side effects in mice and zebrafish. Overall, compound **(16)** demonstrated to be the first Nur77 modulator mediating the TP53 phosphorylation pathway, which has the potential as a novel anti-cancer agent for TNBC.



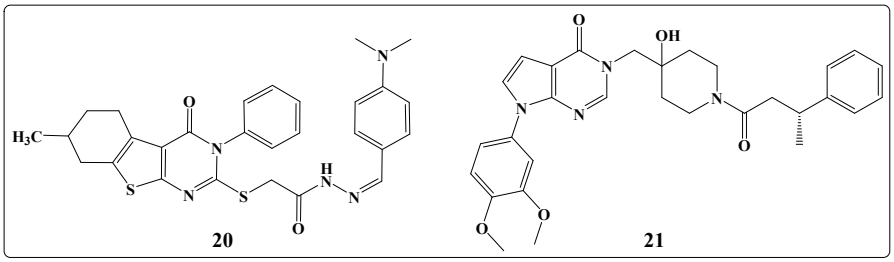
17

Zeng et al reported a series of N-(pyridin-3-yl) pyrimidin-4-amine derivatives as potent CDK2 inhibitors.[29] Compound **(17)** exhibited broad antiproliferative efficacy against various cancer cells MV4-11, HT-29, MCF-7, and HeLa with IC_{50} values comparable to those of Palbociclib and AZD5438. Compound **(17)** also induced cell cycle arrest and apoptosis in HeLa cells in a concentration-dependent manner. Furthermore, it has exhibited CDK2/cyclin A2 inhibitory activity over AZD5438 with an IC_{50} of 64.42 nM. These facts suggest that the compound **(17)** may serve as a very promising scaffold as a CDK2 inhibitor.



18 **19**

Sun et al reported the synthesis and biological evaluation of a series of ENPP1 inhibitors based on a pyrido[2,3-d]pyrimidin-7-one scaffold.[30] Compound **(18)** showed significant potency in both ENPP1 inhibition and STING pathway stimulation during in vitro optimization efforts. Notably, **(18)** showed in vivo efficacy in a syngeneic 4T1 mouse triple negative breast cancer model. *Ji et al* found that the 3,4-dihydropyrimido[4,5-d]pyrimidine-2(1H)-one scaffold **(19)** exerted significant inhibitory potency against lymphocyte-specific protein tyrosine kinase (Lck) with an IC_{50} value of 10.6 nM.[31] Also, compound **(19)** showed high efficacy in various colon cancer cell lines as indicated by GI_{50} values ranging from 0.24 to 1.26 μM.



20 **21**

Seif et al synthesized some novel 3-phenyltetrahydrobenzo[4,5]theno[2,3-d]pyrimidine derivatives and screened them for their antiproliferative activity against 60 cancer cell lines.[32] Screening against HCT-116, a colon cancer cell line, and FHC, a normal colon cell line, showed that compound **(20)** had superior activity to doxorubicin. Compound **(20)** was also most potent against B-RAFWT and mutant B-RAFV600E compared to vemurafenib. Cell cycle analysis of compound **(20)** showed that it increased cell population and arrested the cell cycle of HCT-116 cancer cells at the G0-G1 stage by 1.23-fold. In the apoptosis assay, compound **(20)** showed an 18.18-fold elevation in overall apoptosis of HCT-116 cancer cells compared to control. *Zhuang et al* reported that pyrrole[2,3-d]pyrimidin-4-one derivatives were potent USP7 inhibitors as well as antiproliferative agents against four types of cancer cell lines.[33] Compound **(20)** effectively inhibited the downstream USP7 pathway and resulted in the accumulation of both p53 and p21 in a dose-dependent manner. Furthermore, compound **(20)** disrupted cell cycle progression by inhibiting the G1 phase and induced significant apoptosis in CHP-212 cells.

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