REVIEW ON THE SIGNIFICANCE OF PYRIMIDINE DERIVATIVES AS POTENT ANTI-ANGIOGENIC VEGFR-2 INHIBITORS

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ABSTRACT

Cancer is a disease in which human cells grow uncontrollably and spread to other body parts. Cancer is the second leading cause of death globally and accounted for 9.6 million deaths in 2022 according to the statistics of the World Health Organization. Cancer can begin in any part of the human organs when the normal cell loses the ability to control the division cycle, which may inhibit apoptosis. Cancer cells grow and multiply by activating the angiogenetic factors to build new capillaries that can supply tumor tissue with nutrients. Cancerous tumors spread into or invade nearby tissues and can travel to other organs in the body to form new carcinogenic tissue by metastasis. The goal of treatment is control growth of cancer cells, and induction the programmed cell death. Pyrimidines and its derivatives have been found as effective and valuable pharmacophoric units in medicinal chemistry to design and develop a wide range of bioactive compounds. The present review summarizes the advances in lead compounds of pyrimidines hybrids and their related heterocycles in the treatment of cancer. Moreover, the review also helps to intensify the drug development process by providing an understanding of the potential role of these hybridized pharmacophoric features as VEGFR-2 inhibitors.

Abbreviations

Abbreviation	Meaning
FGFR1	Fibroblast growth factor receptor 1
VEGFR	Vascular Endothelial Growth Factor
CSF-1R	Colony stimulating factor 1 receptor
NETs	Neuroendocrine tumors
AKT	Protein kinase B (PKB), also known as Akt
A549	Human lung adenocarcinoma cell line
MCF-7	Human breast cancer cell line
HepG2	Human liver cancer cell line
Ovcar-3	High-grade serous ovarian adenocarcinoma cell line

Objectives

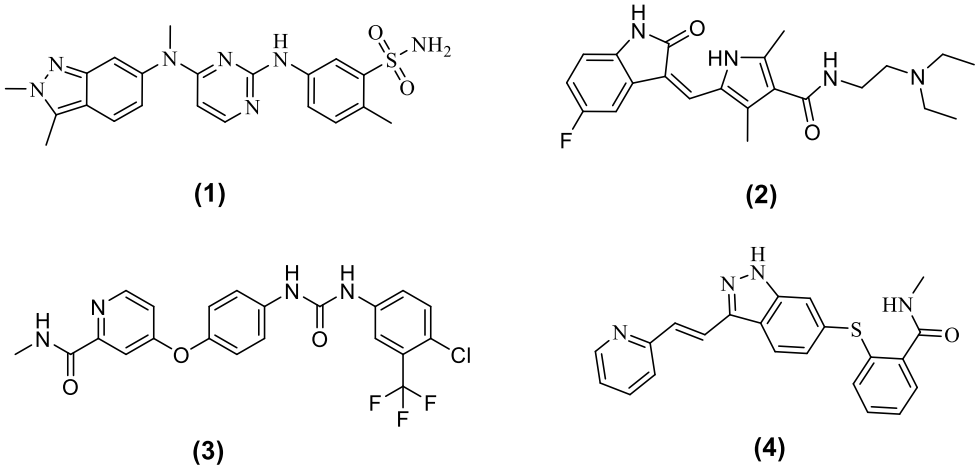
The aim of this study is to highlight the role of Pyrimidines containing compounds in inhibiting VEGFR-2 as well as to suggest some new aspects of treatment

of cancer using pyrimidines scaffold soon.
Keywords: Pyrimidines, Cancer, Drug design, Pharmacophore.

1. Introduction

Angiogenesis, the formation of new blood vessels from preexisting vasculature, is an essential process for cell development and reproduction (Folkman 1995, Kerbel 2000). Considering the similar function in cancerous cells, uncontrolled or abnormal angiogenesis has been linked to tumor progression and metastasis (Behdani, Zeinali et al. 2012). Therefore, finding efficient anti-angiogenesis agents could be considered as one of the main strategies for cancer treatment (Lee, Tan et al. 2018).

Growth factors, including vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs), play a key role in angiogenesis regulation (Traxler and Furet 1999, Chen, Kovar et al. 2005, Cui, Tran-Dubé et al. 2011). Three main vascular endothelial growth factor receptor subtypes are well defined. Amongst, VEGFR-2 receptor is mainly responsible for cell proliferation, vascular permeability, cell migration, and cell survival through VEGF-induced signaling in endothelial cells (Olsson, Dimberg et al. 2006). Activation of VEGFR-2 receptor by VEGF results in a cascade of signaling pathways result in tumor angiogenesis (Kang, Pang et al. 2018). Tyrosine kinase inhibitors (TKIs) are small molecules that can easily enter cells and subsequently hinder the VEGF/VEGFR-2 signaling pathway or, at least, reduce its response (El-Helby, Sakr et al. 2019). Over the last years, several small molecules have been approved for blocking this critical pathway in angiogenesis (Claesson-Welsh and Welsh 2013, Alanazi, Mahdy et al. 2021). Development of tumor resistance to the effect of the current clinically used small-molecule TKIs opens the door for investigation of the effectiveness of new chemotypes. At present, many small molecule VEGFR-2 inhibitors have been synthesized and approved to be potent anti-cancer agents, such as Pazopanib **1**, Sunitinib **2**, Sorafenib **3**, and Axitinib **4 Fig. 1**.

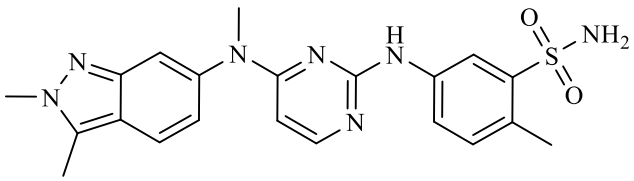


Pyrimidine and its derivatives have been found to be effective and versatile pharmacophoric units in medicinal chemistry to design and develop a wide range of bioactive compounds. However, it has been shown to possess a potential inhibitory

effect against VEGFR-2 enzyme. Thus, it has been widely incorporated in several small molecules that efficiently act as anti-angiogenic agents.

1.1. Approved Pyrimidine derivatives as VEGFR-2 Inhibitors in cancer therapy.

Different pyrimidine derivatives have been approved as VEGFR-2 inhibitors. Pazopanib **1** (Votrient®) (Harris, Boloor et al. 2008) is a highly active VEGFR-2 inhibitor. It was approved by FDA for treatment of RCC and soft tissue sarcoma (Bukowski, Yasothan et al. 2010).



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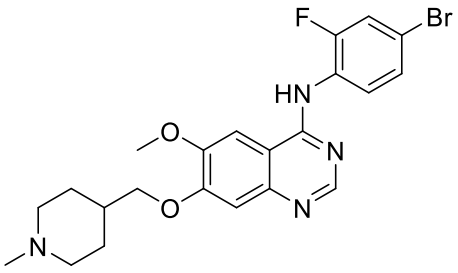
Vandetanib **5** (Caprelsa®) was designed to inhibit VEGFR-2, EGFR and RET-TS (Morabito, Piccirillo et al. 2010). In April 2011, vandetanib became the first drug to be approved and documented by the FDA as a promising treatment for late-stage (metastatic) medullary thyroid cancer in adult patients who are ineligible for surgery (Commander, Whiteside et al. 2011).



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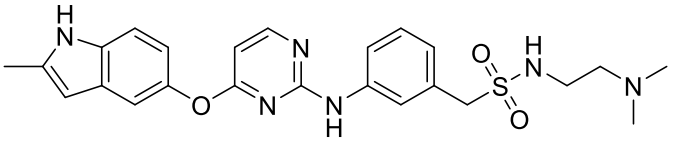
1.2. Pyrimidine derivatives as VEGFR inhibitors in clinical trials.

Surufatinib **6** (Sulanda®), an oral angio-immunokinase inhibitor that selectively targets FGFR1, VEGFR 1, 2, and 3, and CSF-1R, is being designed and developed for the treatment of solid tumors, including neuroendocrine tumors (NETs). Currently, surufatinib **6** is approved for the treatment of pancreatic NET in China and for treatment of pancreatic and extra pancreatic NET in the USA; phase II trials are under way for other solid cancers, including biliary tract carcinoma, thyroid cancer, and soft tissue sarcoma (Syed 2021).



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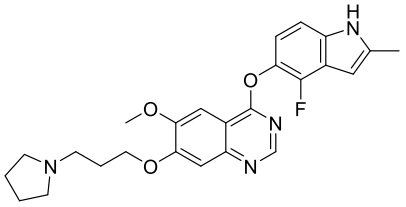
Cediranib (AZD2171) **7** is an active inhibitor of VEGFRs, showing IC_{50} values of 5, 1 and 3 nM toward VEGFR-1, -2 and -3, respectively (Wedge, Kendrew et al. 2005).

AZD-2932 **8** is a potent inhibitor of VEFGR-2 and PDGFRβ with IC_{50} values of 8 and 4 nM, respectively (Plé, Jung et al. 2012).

Fruquintinib **9**, was designed to be highly selective on small-molecule tyrosine kinase inhibitor of VEGF receptors (VEGFRs)-1, -2, and -3, it has been approved and relied in China by NMPA for the treatment of metastatic colorectal cancer. Currently, fruquintinib is being studied in patients with refractory metastatic colorectal cancer as part of a Phase III study (Dasari, Sobrero et al. 2021).



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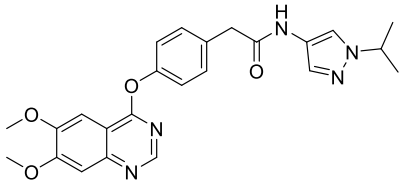

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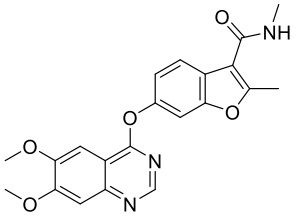

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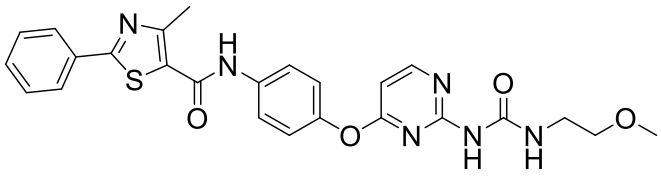
1.3. Promising Pyrimidine derivatives as potent VEGFR-2 inhibitors in literature.

A new class of 4-phenoxy pyrimidine derivatives was developed to inhibit VEGFR-2 enzyme. Various candidates were synthesized by Feiyi Yang *et al.* and tested against different cell lines. In comparison with sorafenib, compound **10** exhibited excellent cytotoxic activity against A549, MCF-7, HepG2 and Ovcar-3 cell lines with IC_{50} values of 2.16, 9.13, 20.15 and 9.65 μM, respectively. It also showed potent inhibitory activity and selectivity against VEGFR-2, with IC_{50} values of 1.05 μM (Yang, Zhang et al. 2022).



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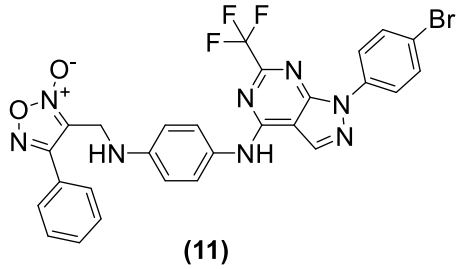
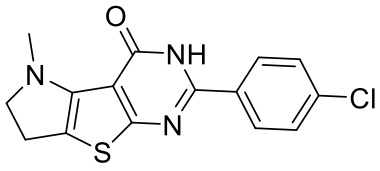
Mater H. Mahnashi *et al*. designed and synthesized series of antiangiogenic pyrazolo[3,4-*d*] pyrimidines. With IC_{50} values of 11.5, 11.6, and 13 µM, the fluorinated compound **11** showed the strongest cytotoxic activity compared to sorafenib against the HepG-2, A2780CP, and MDA-MB-231 cell lines. In addition, compound **11** showed the highest inhibitory effect against VEGFR-2 compared to sorafenib with IC_{50} equal to 0.092 versus 0.049 µM for sorafenib (Mahnashi, El-Senduny et al. 2022).



(11)

Different pyrrolo thieno pyrimidine derivatives were synthesized and optimized as dual VEGFR-2/AKT inhibitors. Many candidates were biologically evaluated. Compounds **12** and **13** had the highest potency and anti-proliferation activity against the tested cell lines HepG-2 and PC-3 with IC_{50} values of 3.023 and 3.12 µM for compound **12** and 3.105 and 2.15 µM for compound **13**. Both compounds were tested against VEGFR-2 and AKT, compound **12** showed the best inhibitory activity with IC_{50} of 0.075 and 4.60 µM, respectively. Furthermore, compound **12** showed a significant apoptotic inducing activity as it arrested the cell cycle at S phase (Abdelnaby, El-Malah et al. 2022).



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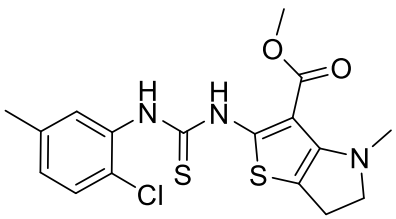
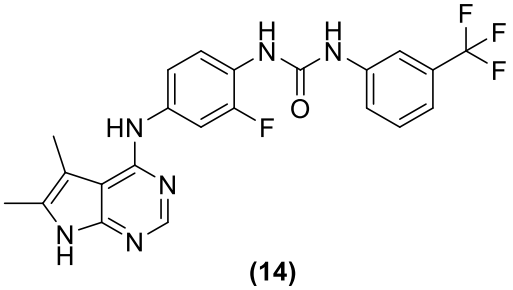


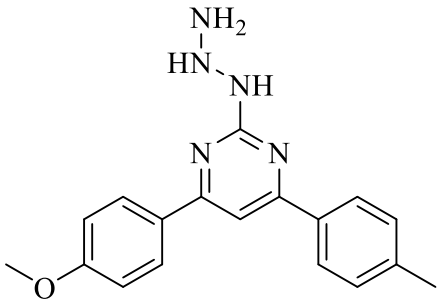
(13)

A congeneric series of novel fluorinated pyrrolo[2,3-*d*] pyrimidine scaffold was designed to mimic regorafenib as VEGFR-2 inhibitor. Candidate **14** showed the best VEGFR-2 inhibitory activity among all the synthesized compounds with IC_{50} equal 52.4 nM. This result was considered better than the reference drug, sorafenib. Compound **14** has fluorine atom near to urea moiety that was responsible for potency of this candidate (Adel and Abouzid 2022).



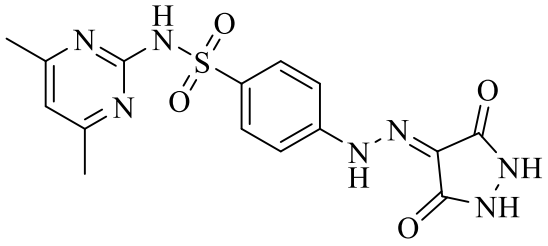
(14)

A series of 4-methoxyphenyl pyrimidine derivatives were synthesized by Abeer M. El-Naggar *et al.* based on the pharmacophoric features of VEGFR-2 and EGFRTK inhibitors in 2022. The highest anti-proliferative activity was observed with compound **15,** as it exhibited cytotoxic activity against HepG-2, MCF-7, MDA-231, HCT-116, and Caco-2, with IC_{50} values of 3.74, 7.81, 4.85, 2.96, and 9.27 µM, respectively. Additionally, it was shown to be the most effective inhibitor against VEGFR-2 and EGFR TK, with IC_{50} values of 0.098 and 0.071 µM compared to erlotinib (IC_{50} = 0.063 µM) and sorafenib (IC_{50} = 0.041 µM) (El-Naggar, Hassan et al. 2022).



(15)

Asmaa M Sayed *et al.* designed and synthesized new pyrimidine sulfonamide derivatives, which was then evaluated as anti-VEGFR-2 candidates. The 3,5-dioxopyrazolidine scaffold exhibited strong activity and selectivity against VEGFR-2, with IC_{50} less than 6.43 µM. Compound **16** was found the most potent derivative that inhibited VEGFR-2 with IC_{50} value of 0.14 µM (Sayed, Taher et al. 2021).



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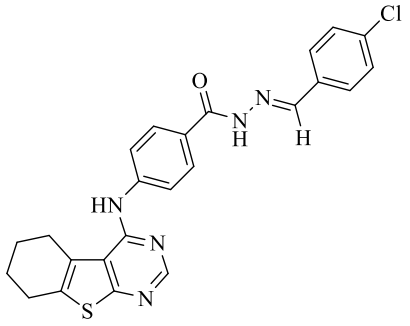
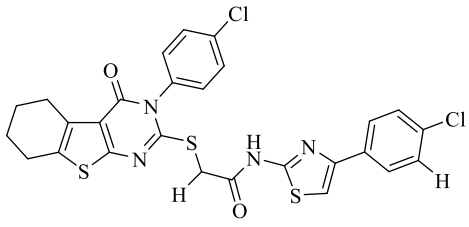
In a study by Souad A. El-Metwally *et al*., compound **17** exhibited the best cytotoxicity against HCT-116 and HepG-2, with IC_{50} values of 2.80 and 4.10 µM, respectively. The most active cytotoxic derivative **17**, with *p*-chloro substitution at the

phenyl hydrophobic tail, displayed an IC_{50} value of 0.23 μM versus sorafenib (IC_{50} = 0.23 μM) as a reference compound (El-Metwally, Abou-El-Regal et al. 2021).



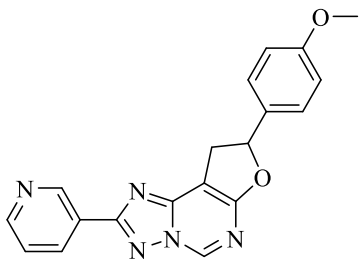
(17)

Yara El-Dash *et al*. synthesized and explored the potential anticancer activities of new hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidines with aminothiazole scaffolds. The primary screening showed that compound **18** displayed potent growth inhibitory effects on CNS cancer cell lines (SNB-75) and renal cancer cell lines (CAKI-1). Compound **18** showed potent inhibitory activity against VEGFR-2 tyrosine kinase with an IC_{50} of 62.48 nM (El-Dash, Elzayat et al. 2021).



(18)

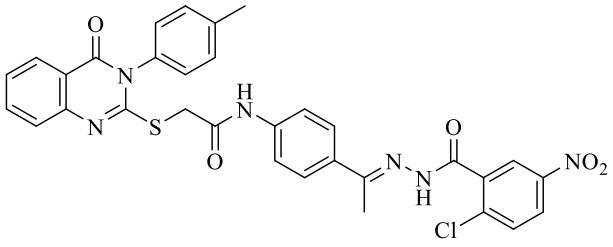
Menna M.A. Abd El-Mageed *et al*. designed and synthesized a new series of furo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives by using fragment-based drug design principles. Compound **19** exhibited the most potent VEGFR-2 inhibitory activity with IC_{50} equal 38.72 nM, versus sorafenib IC_{50} equal 43.31 nM, against VEGFR-2. Additionally, compound **19** showed a significant activity as it arrested the cell cycle at G2/M phase (Abd El-Mageed, Eissa et al. 2021).



(19)

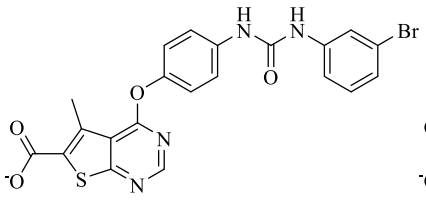
A new series of quinazoline-4(3*H*)-one derivatives were designed and synthesized by Khaled El-Adl *et al.* These candidates were screened against three human cancer cell

lines (HepG-2, MCF-7 and HCT-116) versus sorafenib and doxorubicin as reference drugs. Compound **20**, containing a 2-chloro-5-nitrophenyl group exhibited the highest inhibitory activity against examined cell lines; it was approximately 4.39, 5.73 and 1.96-fold more active than doxorubicin and 3.88, 5.59 and 1.84-fold more active than sorafenib against HepG2, HCT-116 and MCF-7 cells, respectively. Compound **20** showed the most active cytotoxic candidate against VEGFR-2 (El-Adl, El-Helby et al. 2021).



(20)

Eman Z. Elrazaz *et al.* synthesized a new series of thieno[2,3-*d*]pyrimidine as promising VEGFR-2 inhibitors. All the designed candidates showed high similarity with lenvatinib as a lead compound. Among these candidates, compounds **21** and **22** exhibited unexpected potent inhibitory activities against VEGFR-2 with IC_{50} of 5.0 and 3.9 nM, respectively. The most potent candidates have substitution with halogen and the optimum activity was established with chlorine at the *para* and *meta* positions (Elrazaz, Serya et al. 2021).



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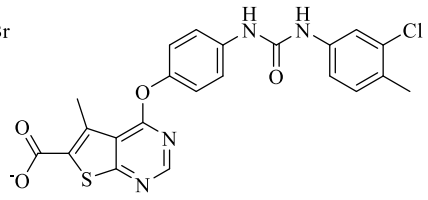
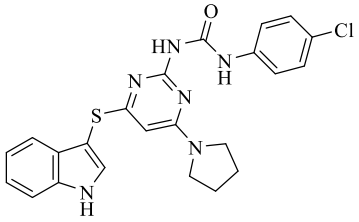


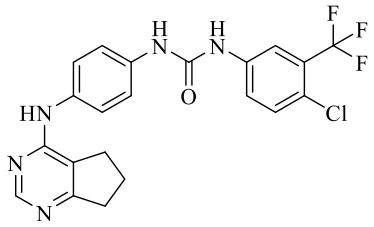
(22)

In 2020, the molecular hybridization between pyrimidine and endol-3-mercapto derivative resulted in a generation of new small molecules that can introduce the highest potency against VEGFR-2. Compound **23** exhibit significant IC_{50} values 5.85, 7.87, 6.41 and 10.43 µM against MDA-MB-231 (breast), HepG2 (liver), A549 (lung) and PC-3 (prostate) cancer cell lines, respectively. Moreover, enzyme inhibition assay was done. Compound **23** showed a high inhibitory action against VEGFR-2 with IC_{50} of 310 nM. Additionally, colony formation and cell migration were tested against compound **23** and showed the ability of compound **23** to inhibit the cell migration (Sana, Reddy et al. 2020).



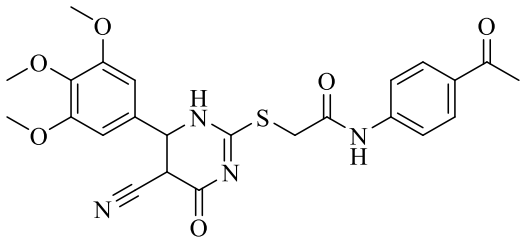
(23)

Mahitab K. Sobhy *et al.* designed and synthesized a new 6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine derivatives as anti VEGFR-2. Based on 3D QSAR model, the new candidates were generated. Among these candidates, compound **24** exhibited the strongest activity and selectivity against VEGFR-2 with IC_{50} less than 0.85 μM (Sobhy, Mowafy et al. 2019).



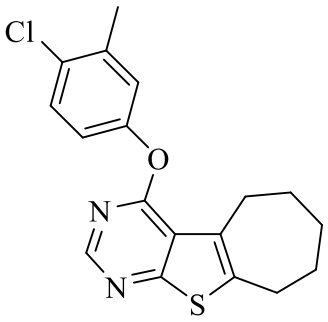
(24)

Adel A. Marzouk *et al*. synthesized a new series of 1,6-dihydropyrimidin-2-thiol derivatives. In a study of leukemia, non-small cell lung cancer, colon, CNS, melanoma, and breast cancer cell lines, compound **25** demonstrated a remarkable anticancer activity. It had an IC_{50} of 19 to 100 μM. The most active inhibitory activity against VEGFR-2 was observed with compound **25**, with a 3,4,5-trimethoxy substitution at the hydrophobic moiety of the phenyl group. With an IC_{50} value of 198.7 nM against VEGFR-2, compound **25** had more significant activity than sorafenib (IC_{50} = 0.17 nM) (Marzouk, Abdel-Aziz et al. 2020).



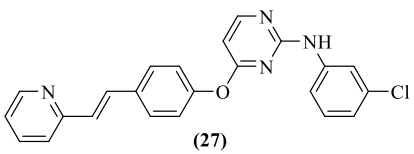
(25)

Mghwary *et al.* synthesized and investigated a new series of novel 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidine scaffold in order to determine their anticancer activity as dual inhibitors of VEGFR-2 and EGFR. Based on the preliminary screening results, compound **26** exhibited strong growth inhibitory effects on MCF-7 cancer cells. It induced cell cycle arrested in G2/M phase and lead to induction of apoptosis (Mghwary, Gedawy et al. 2019).



(26)

Wuji Sun *et al.* designed and synthesized a new pyrimidine-based derivative as anti VEGFR-2. These derivatives were biologically examined against A549 and HepG2 cell lines. compounds **27**, **28** and **29** exhibited excellent inhibitory activities against A549 cell line with IC_{50} ranged from 9.19 to 13.17 μM and HepG-2 cell line with IC_{50} ranged from 11.94 to 18.21 μM compared to a reference drug, Pazopanib (IC_{50} = 21.18 and 36.66 μM) (Sun, Hu et al. 2018).



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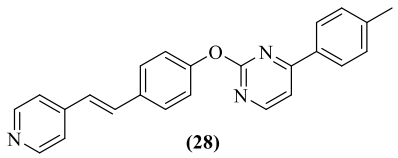

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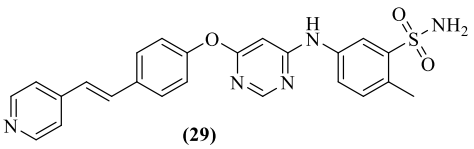

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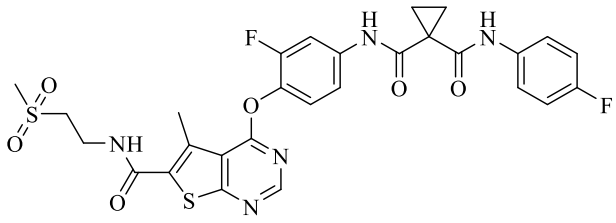
A new series of thieno[2,3-d] pyrimidine scaffold was synthesized by Jiaming Li *et al.* Compound **30** was considered the most potent one, the IC_{50} values of which were 25 and 48 nM for c-Met and VEGFR-2, respectively. These results supported by molecular docking study to show the binding mode of these compounds (Li, Gu et al. 2017).



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مقال عن أهمية مشتقات البيريميدين كمثبطات فعالة لعامل النمو الوعائي ومحفزة لموت الخلايا المبرمج

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نظرا لأن مرض السرطان لايزال من أهم الأمراض وأخطرها على مستوى العالم مما دفع الى تطوير العديد من العقاقير والانظمه الدوائية المتخصصة فى علاجه. وبالبحث والرجوع الى المراجع العلمية المتعددة التى تتناول تشيد مركبات جديده ذات فاعلية مضاده لمرض السرطان وجد لبعض المشتقات الجديدة لنواه البيريميدين فعالية عالية كمثبطات لعامل النمو الوعائي ومحفزة لموت الخلايا المبرمج . وقد تناولنا فى هذا البحث بعض المشتقات لنواه البيريميدين ذات الفعالية العالية فى علاج مرض السرطان .

الكلمات المفتاحية : البيريميدين , السرطان , تصميم الادوية , الادوية المهجنة .