

PYRIDINE DERIVATIVES AS ANTICANCER AGENTS: FDA-APPROVED DRUGS AND PROMISING REPORTED COMPOUNDS

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ABSTRACT

Pyridine derivatives are a family of heterocyclic nitrogenous compounds possessing many of applications in the discovery of anticancer drug. This synthetic category serve as the potent class of compounds in the treatment of many types of tumors as breast cancer, myeloid leukemia, pancreatic cancer, liver cancer. In this review, the recent results of the published studies about pyridine derivatives were reported. In addition, the most promising candidates in each work was focused mentioning it anticancer activity compared to the reference molecules. This work may serve as a collection of promising candidates for further design and synthesis of anti-cancer agents.

Keywords: Pyridine derivative; Anti-cancer agents; Biological targets

1. Introduction

Cancer is a lethal cluster of diseases described by overexcited cell division, it can attack and spread to all tissues of the body through metastasis process causing death (Alsaif *et al.* 2021). Cancer is the leading cause of death worldwide and the biggest obstacle to extending life expectancy in the twenty-first century (Khan *et al.* 2021). According to World Health Organization, the number of cancer cases in the world will be estimated to increase to 22 million by 2030 (Alsaif *et al.* 2021).

Cancer is a multifactorial disease. Although a number of environmental factors also play a role, the genetic changes are a major influence in the development and progression of this complex illness (Azevedo *et al.* 2020). Mutations result from replication errors or from DNA damage that is either left unrepaired or repaired incorrectly (Martincorena *et al.* 2015). DNA damage can be caused by extrinsic factors, including chemicals, UV light, and ionizing radiation; or by intrinsic factors such as enzymes involved in DNA repair or genome editing (Friedberg *et al.* 2005). Environmental factors represents 80–90% of cancer causes, according to epidemiological research, environmental variables resulting from human behavior like smoking, alcohol, diet, and sexual conduct are the primary causes of malignant neoplasia in human population (Lewandowska *et al.* 2018). Infections brought on by certain fungi, bacteria, or viruses are risk factors for the development of cancer. Infection with oncogenic pathogens causes 15% of malignancies worldwide. Particularly, by incorporating oncogenes into the host genome, human oncoviruses can promote carcinogenesis (Azevedo *et al.* 2020).

Uncontrolled cell proliferation occurs during carcinogenesis and is brought on by the activation of oncogenes or the inactivation of tumor suppressor genes. Down-regulation of cell adhesion receptors required for tissue-specific cell-cell attachment and up-regulation of cell motility-enhancing receptors are both necessary for metastasis. These traits can be altered by epigenetic modifications, including as histone alterations, DNA methylation, and DNA hydroxymethylation. MicroRNA and the signaling pathways that control apoptosis and autophagy are targets for these epigenetic modifications. We suggest that predisposed normal cells change into cancer progenitor cells, which then proliferate and shift from epithelial to mesenchymal tissue. Both progenitor and fully developed cancer cells may develop into a metastatic form as a result of this partially epigenetic process, which may then cause metastasis to a distant site (Sarkar *et al.* 2013).

Traditional cancer treatment methods include chemotherapy, radiation therapy, immunotherapy, and surgery. Along with surgery and radiation, immunotherapy and chemotherapy are frequently employed. The simultaneous use of numerous anticancer medications with distinct modes of action is more beneficial than using a single agent, with the benefits being enhanced efficiency of action, less toxicity, and evasion of drug resistance. Additionally, a combination of two or more chemotherapeutic drugs may be required (Patrick 2013).

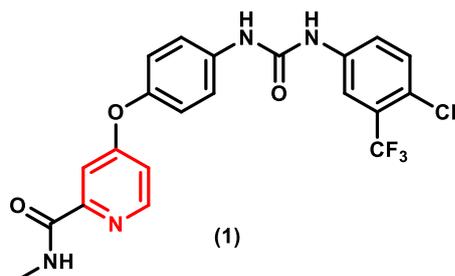
Chemotherapy is one of the most popular anticancer treatments and uses potent cytotoxic medications to target rapidly dividing cells in the body in order to limit the growth of tumors (Brianna *et al.* 2023). The initial applications of nitrogen mustards and antifolate medicines in the 1940s marked the beginning of the age of chemotherapy. Since that time, the discovery of cancer drugs has gone from being a low-budget, government-supported research project to a risky, multi-billion dollar industry (Chabner *et al.* 2005). Despite its recognized negative consequences on the patient's physical and mental health, chemotherapy is nevertheless a frequently chosen therapeutic choice (Anand *et al.* 2022).

Based on the mechanism or therapeutic target that they work on, chemotherapeutic drugs can be divided into a variety of classes, such as alkylating agents (Patrick 2013), intercalating agents (Avendaño *et al.* 2008), and antimetabolites (Patrick 2013)(Avendaño *et al.* 2008). In this work, the pyrimidine derivatives as anticancer agents were summarized from 2004 until 2023.

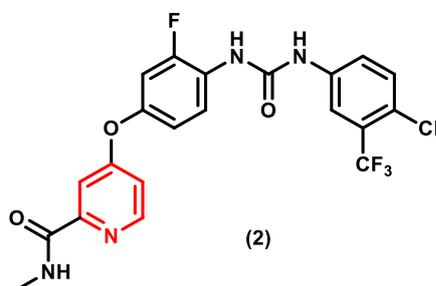
2. Pyridine derivatives as anticancer agents

2.1. Some FDA-approved Pyridine derivatives for the treatment of cancer

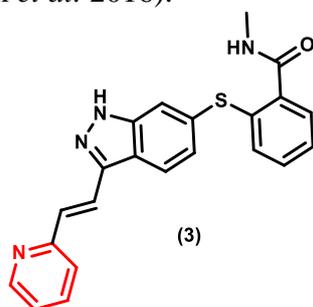
For the treatment of advanced renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC), sorafenib **1** (Nexavar®) received approval in 2005 (Woo *et al.* 2012). Raf, VEGFR, PDGFR, and KIT are just a few of the kinases that sorafenib, a diaryl urea multiple-targeted anticancer drug, is able to block. VEGFR-2 and VEGFR-3 are inhibited by sorafenib (Wilhelm *et al.* 2006). More and more researchers are concentrating on the optimization of sorafenib due to the benefits of multi-mechanisms, broad-spectrum anticancer activity, and well-tolerated results in combination trials (Yao *et al.* 2012).



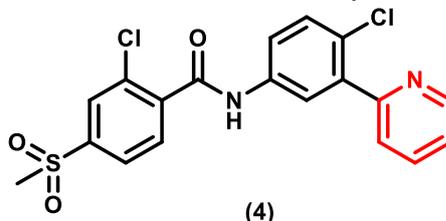
Regorafenib **2** (Stivarga®), is a fluoro derivative of sorafenib, developed by Bayer and approved in 2012 (Wilhelm *et al.* 2007). It inhibits angiogenic kinases (VEGFR-1/3, PDGFR β , FGFR1, and the mutant oncogenic kinases Kit, RET, and B-Raf with IC₅₀ values in the low nanomolar range. The compound shows anti-proliferative effects on different cancer cell lines and is active in various preclinical human xenograft models in mice, where it also demonstrated antiangiogenic activity (Wilhelm *et al.* 2011).



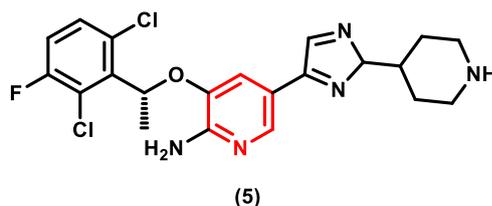
Axitinib **3** (Inlyta®), which had been previously treated for RCC patients who had not responded, received FDA approval in January 2012. It is a specific inhibitor of the VEGFR1, VEGFR2, and VEGFR3 receptors, which play a role in both healthy and malignant angiogenesis. (Karam *et al.* 2016).



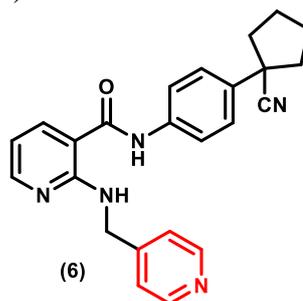
Vismodegib **4**, was approved by the US Food and Drug Administration (FDA) for the treatment of basal cell carcinoma (BCC) in January 2012. (Dlugosz *et al.* 2012)



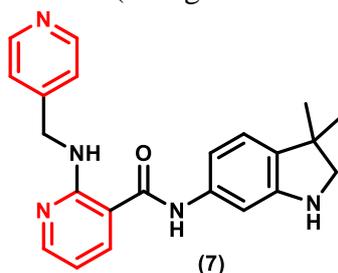
In August 2011 crizotinib **5** (Xalkori; Pfizer), a small-molecule kinase inhibitor, was approved by the (US) FDA for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer that is anaplastic lymphoma kinase-positive, as detected by an FDA-approved test (Shaw *et al.* 2011).



Apatinib **6**, a tyrosine kinase inhibitor, can specifically inhibit vascular endothelial growth factor receptor 2, showing encouraging anti-tumor effects in a variety of tumors including advanced hepatocellular carcinoma (HCC). It has been approved in 2017 (Zhang *et al.* 2020).

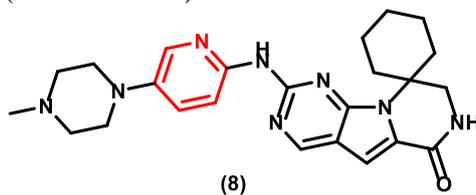


Motesanib **7**, a nicotinamide derivative, was identified as a potent, orally bioavailable inhibitor of the (VEGFR1/Flt1), VEGFR2//Flk-1, VEGFR3/Flt4, (PDGFR) and Kit receptors in preclinical models (Wang *et al.* 2014).

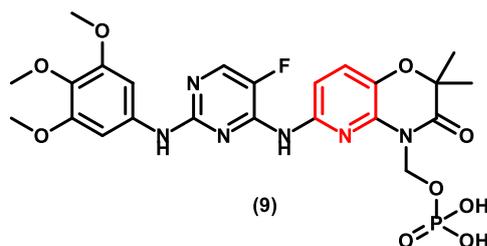


According to reports (Altaf *et al.* 2015, Albratty *et al.* 2022), pyridinoids are a type of heterocyclic nitrogenous chemicals with a wide range of biological activity. They showed outstanding anticancer and immunomodulatory properties.

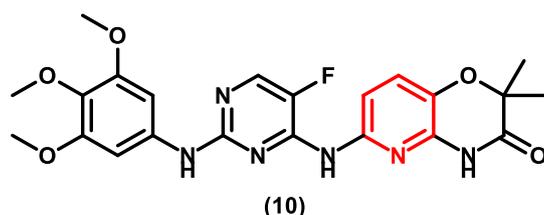
A CDK4 and CDK6 inhibitor called trilaciclib **8** is recommended for patients with advanced stages of small cell lung cancer in order to decrease the likelihood of chemotherapy-induced myelosuppression before receiving topotecan- or platinum- and etoposide-containing chemotherapy. It was approved on February 12th, 2021 by the FDA (Powell *et al.* 2021) (Dhillon 2021).



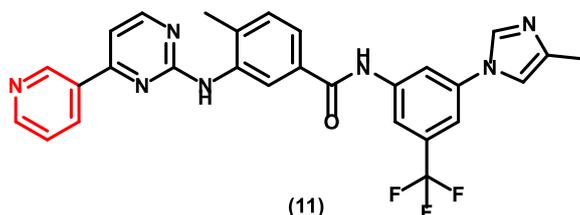
After failing at one other treatment, fostamatinib **9** is a spleen tyrosine kinase inhibitor used to treat chronic immune thrombocytopenia. Fostamatinib has been studied for the treatment and underlying science of immune thrombocytopenic purpura (ITP) and rheumatoid arthritis. It has been approved in 2018 (Newland *et al.* 2018, Mehta *et al.* 2022).



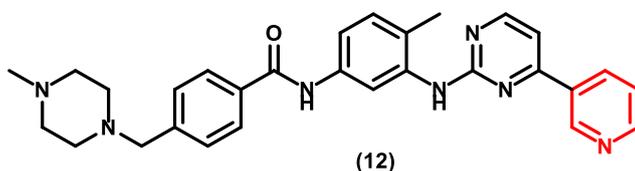
The FDA authorized tamatinib **10** in 2018 to treat chronic idiopathic thrombocytopenic purpura (ITP). For autoimmune hemolytic anemia, RA, lymphoma, and immunoglobulin A nephropathy, this medication has undergone clinical trial testing (Markham 2018).



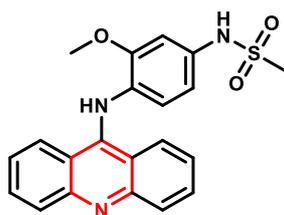
Nilotinib **11**, Bcr-Abl tyrosine-kinase inhibitor, was approved in 2007 for the treatment of newly diagnosed or imatinib-resistant or -intolerant chronic myelogenous leukemia (CML) and has shown superiority over imatinib in first-line treatment for newly diagnosed CML (Tanaka *et al.* 2010, Blay *et al.* 2011). Nilotinib has an immunomodulatory effect and inhibits CD8⁺ T cell function (Chen *et al.* 2008).



Imatinib **12**, was approved in 2001 and confirmed to have immunomodulatory functions (Cohen *et al.* 2002, Leder *et al.* 2007). It causes lymphopenia and decreases immunoglobulin levels (Cwynarski *et al.* 2004). Due to its immunomodulatory effect, imatinib was considered a potential treatment for COVID-19 (Morales-Ortega *et al.* 2020).



Amsacrine (m-AMSA) **13** is an anticancer agent that displays activity against refractory acute leukemias as well as Hodgkin's and non-Hodgkin's lymphomas. The drug is comprised of an intercalative acridine moiety coupled to a 4'-amino-methanesulfon-*m*-anisidide headgroup. m-AMSA is historically significant in that it was the first drug demonstrated to function as a topoisomerase II poison (Ketron *et al.* 2012).

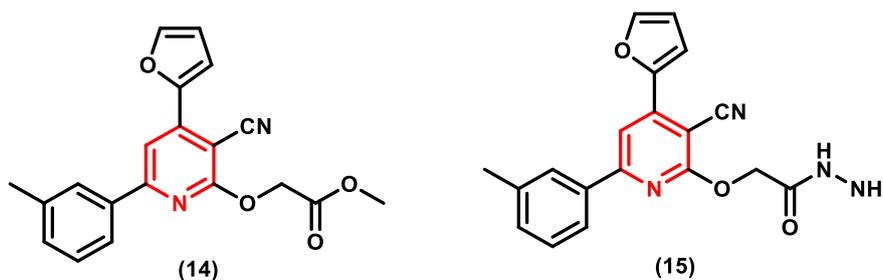


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2.2. Pyridine derivatives as anticancer agents in literature

2.2.1. Pyridine as topoisomerase inhibitors

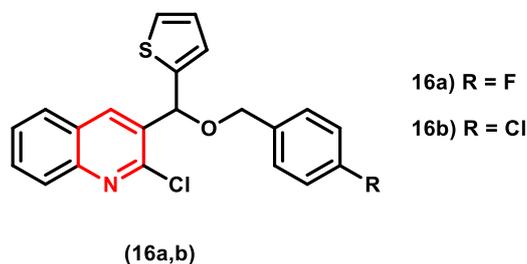
Thirteen poly-heterocyclic compounds containing pyridine moieties were synthesized by Kadi *et al.* The cytotoxicity of all compounds was assessed *in vitro* against MCF-7 and A-2780 cell lines using the MTT assay. Among them, compounds **14** and **15** at 0.1 μM concentration showed more potent cytotoxicity against the MCF-7 and A-2780 cells than the reference drug docetaxel. The docking studies revealed an excellent affinity against the active site of the human topoisomerase enzyme, which may explain the promising cytotoxicity of these classes of molecules (Kadi *et al.* 2023).



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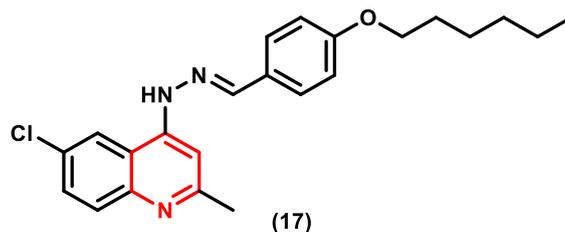
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Othman *et al.* synthesized some interesting thiophene-pyridine hybrids. Compounds **16a,b** showed potent and selective cytotoxic activity against MCF-7 cell line ($\text{IC}_{50} = 38.41$ and $28.36 \mu\text{M}$, respectively) and remarkable *in vitro* Topoisomerase II inhibitory activity ($\text{IC}_{50} = 0.23$ and $0.44 \mu\text{M}$, respectively). Such activity was higher than that of the reference compound (topotecan) ($\text{IC}_{50} = 0.48 \mu\text{M}$) (Othman *et al.* 2019).

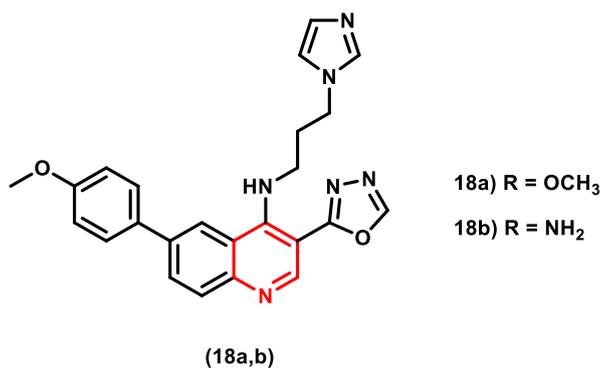


(16a,b)

Katariya and co-workers developed a series of 2,4- substituted-6-halogenated pyridine derivatives. Compound **17** emerged as the most promising candidate. *In vitro* screening performed against the full panel of sixty human cancer cell lines of the NCI, showed an interesting anti-proliferative activity with IC_{50} values in the 0.3-2.05 mM range. Molecular docking analysis supported the hypothesis of Topoisomerase as a putative target of compound **17** (Katariya *et al.* 2020)



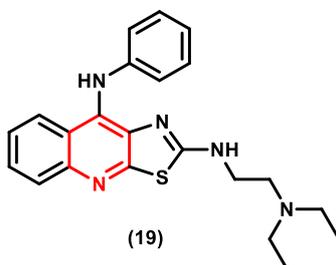
Recently, Kundu *et al.* designed and synthesized the non-intercalating Topoisomerase-targeting compounds **18a,b**. These compounds showed an excellent Topo II IC₅₀ of 29 and 24 Nm, respectively (Kundu *et al.* 2019, Kundu *et al.* 2020).



2.2.3. Pyridine derivatives as DNA intercalators

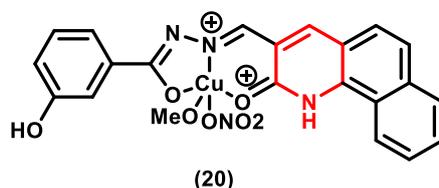
DNA intercalators are generally characterized by polycondensed aromatic ring systems. This flat molecular moiety is able to insert itself between the planar base pairs of DNA, with consequent perturbation of double helix, strand breaks and cytotoxicity. Due to the electronic and steric features, pyridine is a recurrent scaffold in intercalating agents.

Among the DNA-binding agents, compound **19** was discovered by Rodrigues *et al.* It showed a potent cytotoxic effect against numerous cancer cell lines (GI₅₀ in the range of 15.9-37.7 μM), with binding to DNA in the nanomolar concentration rang (Rodríguez-Loaiza *et al.* 2004).



Ramachandran *et al.* developed a set of 2-oxo-1,2-dihydrobenzo [h]quinoline-3-carbaldehyde derivatives as copper (II) complexes with improved biological activity. Compound **20** is one of the most interesting member in the series exhibiting capability

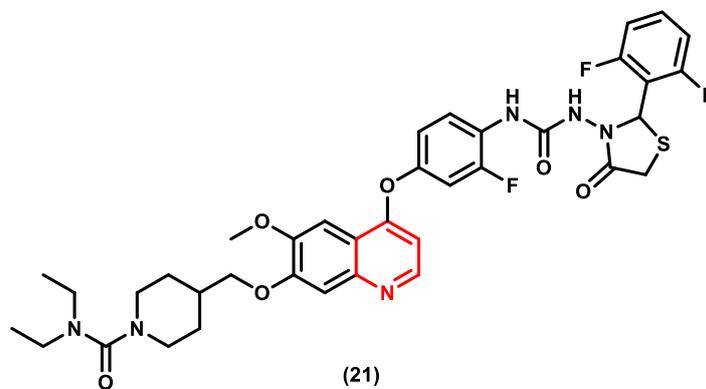
to intercalate DNA. It showed a potent cytotoxic activity in a low micromolar range, especially against MCF-7 cell line ($IC_{50} = 0.05 \mu\text{M}$) (Ramachandran *et al.* 2018).



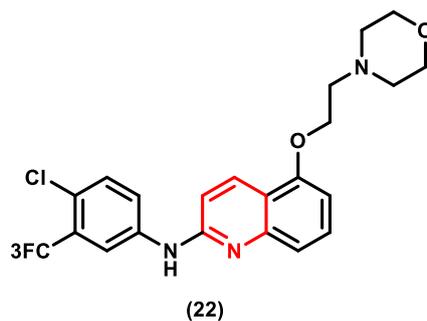
2.2.4. Pyridine derivatives as tyrosine kinase inhibitors

Tyrosine kinase proteins play a role in cell development, differentiation, and death, as well as a variety of physiological and biochemical activities. PTK expression abnormalities may influence carcinogenesis, tumor invasion, and secondary tumor, tumor neovascularization, and tumor treatment resistance (Wang *et al.* 2014).

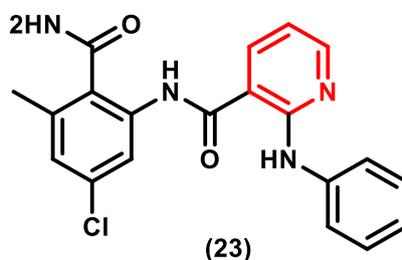
Zhou *et al.* reported the production of 1-benzopyridine derivatives based on thiazolidinone. Based on the findings of the biological assessment and docking investigation, **21** compound demonstrated good antitumor activity on human colorectal adenocarcinoma cells. It had toxicity to normal cells of 10.01 g/mL, indicating that it was considerably less than Regorafenib. This molecule may act as an effective starting point for the creation of high powerful kinase inhibitors as antitumor medicines in the future, with further structural modification to increase inhibitory action (Zhou *et al.* 2021).



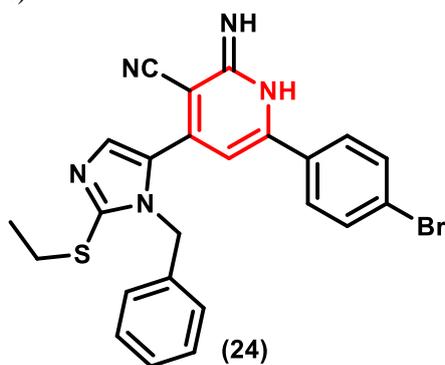
El-Damasy *et al.*, designed and synthesized compounds with benzopyridine moiety. The majority of the substances examined had an anti-proliferative activity that was both strong and wide in the spectrum. Compound **22** was evaluated towards a board of 47 oncogenic kinases, and antitumor effects have been assessed towards sixty tumor cell lines. This compound has more potential than gefitinib during the several tested cell lines (El-Damasy *et al.* 2016).



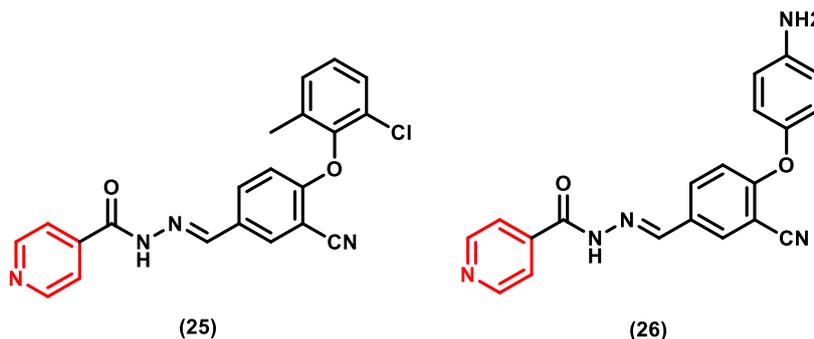
In 2017, a series of diamides derivatives containing nicotinamide unit were designed, synthesized, and evaluated by Min Peng *et al* for their potential cytotoxic activities against human cancer cell lines. Compound **23** exhibited the highly potential inhibitory activities against NCI-H460 cell line with the IC_{50} values of $4.07 \mu\text{g/mL}$, which might be developed as novel lead compounds for potential cytotoxic agents (Peng *et al.* 2017).



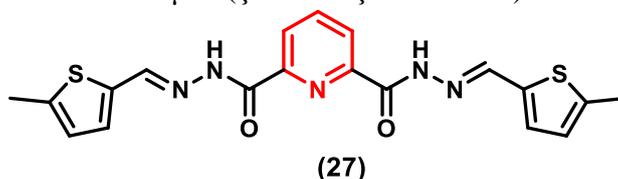
Derivatives of 6-aryl-4-imidazolyl-2-imino-1,2-dihydro-pyridine-3-carbonitriles were synthesized by Davari *et al.* The synthesized compounds were evaluated for their PDE3A inhibitory effects, as well as their cytotoxic effects on MCF-7 and HeLa cell lines. Compound **24** exhibited the strongest PDE3A inhibitory effects with an IC_{50} of 3.76 nM (Davari *et al.* 2014).



Different molecules have been designed and synthesized with the pyridine moiety by Nippu *et al.* The *in vitro* cell viability of **25** and **26** on the pancreatic cancer cell line MIA PaCa-2 exhibits IC_{50} values of 36.03 and $38.76 \mu\text{M}$, respectively (Nippu *et al.* 2023).



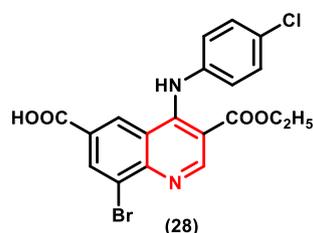
Pyridine-based dihydrazones derivatives were synthesized by Senkardes *et al.* The synthesized compounds were screened for their anticancer activities. Compound **27** exhibited promising activity against Ishikawa human endometrial cancer cell line (ISH) with an IC_{50} value of 8.26 μ M (Şenkardes *et al.* 2021).



2.2.5. Pyridine derivatives as EGFR inhibitors

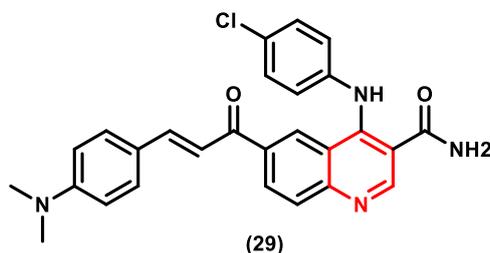
The tyrosine kinase receptor family, which includes the epidermal growth factor receptor (EGFR), is a cell-proliferative signaling mechanism found in cancer cells. These receptors are widely distributed in cell membranes and frequently have an impact on a number of processes, including cell growth, cell death, and cell multiplication. This protein significantly contributes to the formation and development of numerous solid cancer types, including breast, lung, colorectal, neck, and head malignancies (Guardiola *et al.* 2019).

In 2017, some pyridine derivatives have been developed by Abdellatif *et al.* Cytotoxic activity of all produced compounds was tested towards breast and lung cancer. The tested compounds exhibited a wide variety of activity against MCF7 and A549 cell lines. Compound **28** ($IC_{50} = 3.42$ and 5.97 μ M) was shown to be highly potent towards both breast and lung tumor cell lines. Furthermore, molecular docking investigations were undertaken, with the results correlating with the *in vitro* cytotoxic data (Abdellatif *et al.* 2017).



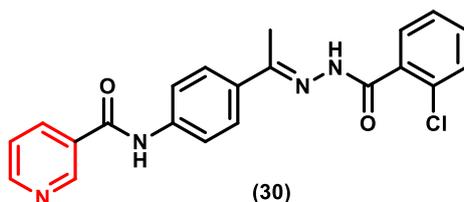
Ibrahim *et al.* have developed a series of compounds with pyridine moiety. All derivatives were tested against breast cancer but only the compound **29** showed substantial activity toward breast cancer. The early results showed that carboxamide-based compound showed a powerful inhibitory effect in cancer development and highly

powerful property on the EGFR TK enzyme having 67% growth inhibition comparison with ATP, which might be a promising antitumor drug (Vickers 2017).

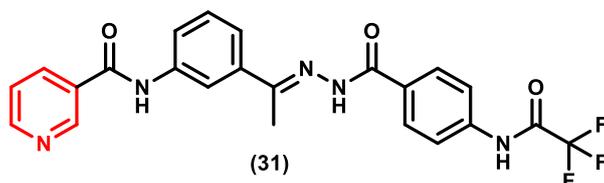


2.2.6. Pyridine derivatives as VEGFR inhibitors

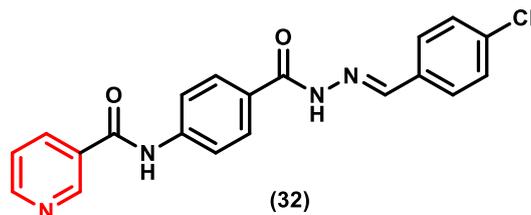
In 2022, Yousef *et al.* designed and synthesized nicotinamide derivatives based on the essential features of the VEGFR-2 inhibitors. Compound **30** revealed the highest anti-proliferative activities with IC_{50} values of 15.4 and 9.8 μM against HCT-116 and HepG2, respectively compared to sorafenib ($IC_{50} = 9.30$ and 7.40 μM) (Yousef *et al.* 2022).



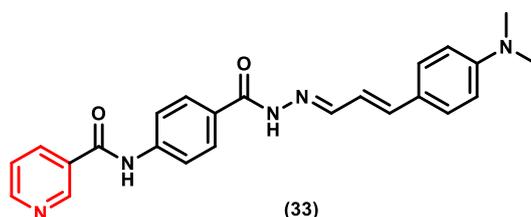
Another pyridine derivative **31** was discovered by Yousef *et al.* It displayed VEGFR-2 inhibition with an IC_{50} value of 65 nM with potent cytotoxic properties against hepatic (HepG2) and breast (MCF-7) cancer cell lines with IC_{50} values of 21.00 and 26.10 μM , respectively. Such compound exhibited high selectivity indices against the normal cell lines (W-38) of 1.55 and 1.25, respectively. The obtained results present compound **31** as a lead VEGFR-2 inhibitor for further biological investigation and chemical modifications (Yousef *et al.* 2022).



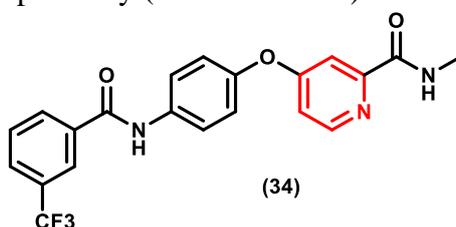
In 2022, Elkaeed *et al.* designed four nicotinamide-based derivatives as antiangiogenic VEGFR-2 inhibitors. All members were evaluated for their cytotoxic and VEGFR-2 inhibitory potentialities. Compound **32** was the most potent member showing IC_{50} values of 9.3 and 7.8 μM against HCT-116 and HepG-2 cells, respectively, and IC_{50} of 60.83 nM regarding VEGFR-2 enzyme inhibition. Additionally, the immunomodulatory effect of compound **32** was verified by significant decrease in TNF- α and IL6 by 66.42% and 57.34%, respectively (Elkaeed *et al.* 2022).



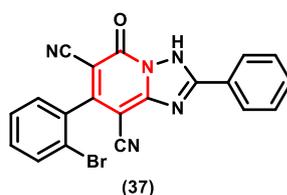
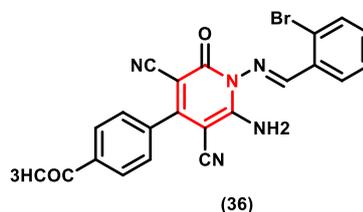
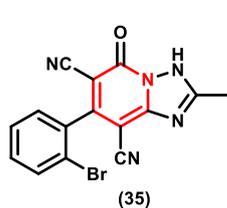
Furthermore, a set of nicotinamide derivatives were synthesized to be VEGFR-2 inhibitors. The cytotoxic efficacy as well as the VEGFR-2 inhibitory activities were determined for the titled compounds. Compound **33** exhibited the strongest anti-proliferative activities with IC_{50} values of 5.4 and 7.1 μ M against HCT-116 and HepG2, respectively. Interestingly, compound **33** was the most potent VEGFR-2 inhibitor with an IC_{50} value of 77.02 nM (compare to sorafenib: $IC_{50} = 53.65$ nM). (Yousef *et al.* 2022).



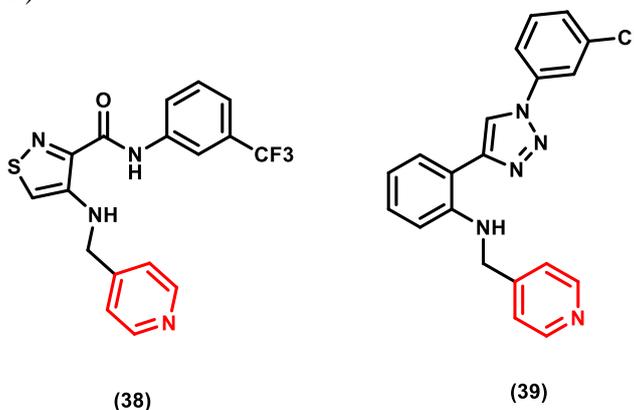
N-methyl-4-(4-(3-(trifluoromethyl) benzamido) phenoxy) picolinamide **34** was created by Cao *et al.* In biochemical kinase experiments, this substance effectively inhibits human tumor angiogenesis-related tyrosine kinase VEGFR-2, fibroblast growth factor receptor 2 (FGFR2), and platelet-derived growth factor receptor (PDGFR) at rates of 97%, 65%, and 55%, respectively (Cao *et al.* 2011).



Novel pyridine-derived compounds were designed and synthesized as VEGFR-2 inhibitors. Their anticancer activities were evaluated against HepG2 and MCF-7 cells. Compounds **35**, **36**, and **37** were found to be the most potent derivatives against the two cancer cell lines, HepG2 and MCF-7, respectively, with IC_{50} values ranging from 4.25, to 12.83 μ M (Saleh *et al.* 2021).



3,4-Disubstituted isothiazoles and (1,2,3-triazol-4-yl)benzenamines derivatives containing pyridine moieties **38** and **39** were synthesized by Kiselyov *et al.* and evaluated for their anti-VEGFR activity. These compounds are potent VEGFR-1 and -2 inhibitors with activity comparable to that of vatalanib in enzymatic and cell assays (Kiselyov *et al.* 2009).



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مشتقات البيريدين كمضادات محتملة للسرطان

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مشتقات البيريدين هي عائلة من المركبات النيتروجينية الحلقية غير المتجانسة التي تمتلك العديد من التطبيقات في اكتشاف أدوية جديدة مضادة للسرطان. تعمل هذه الفئة المخالفة كقوة قوية من المركبات في علاج العديد من أنواع الأورام مثل سرطان الثدي وسرطان الدم النخاعي وسرطان البنكرياس وسرطان الكبد. في هذا البحث المرجعي، تم استعراض النتائج الحديثة للدراسات المنشورة حول مشتقات البيريدين. بالإضافة إلى ذلك، تم التركيز على المركبات الواعدة في كل عمل على ذكر نشاطه المضاد للسرطان مقارنة بالمركبات المرجعية. قد يكون هذا العمل بمثابة تجميع للمركبات الواعدة لمزيد من التصميم والتوليف لعوامل جديدة مضادة للسرطان.

الكلمات المفتاحية: مشتقات البيريدين، مضادات السرطان، الأهداف البيولوجية.