VEGFER-2 INHIBITORS AND QUINAZOLINE-BASED ANTICANCER AGENTS

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ABSTRACT

Inhibitors of vascular endothelial growth factor receptor -2 (VEGFR-2) are crucial biological targets for the development of novel anticancer medications. Quinazoline also plays an important role as one of the building elements of numerous anticancer drugs. Thus, a review of the literature on VEGFR-2 inhibitors and Quinazoline-based anticancer medicines has been completed. We introduced VEGFR-2 inhibitors now undergoing clinical evaluation, such as Gefitinib, Erlotinib, Vandetanib, Afatinib, Lenvatinib, Cabozantinib, Sorafenib and Regorafenib in our survey. Additionally, VEGFR-2 inhibitors that are under development were introduced.

Keywords: Vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitors; Quinazoline; Anti-cancer agents

1. Introduction

Cancer is a major public health problem worldwide and is the second leading cause of death. In 2020, the diagnosis and treatment of cancer was hampered by the coronavirus disease 2019 (COVID-19) pandemic. For example, reduced access to care because of health care setting closures resulted in delays in diagnosis and treatment that may lead to a short-term drop in cancer incidence followed by an ultimately increased mortality (Rebecca *et al.* 2021).

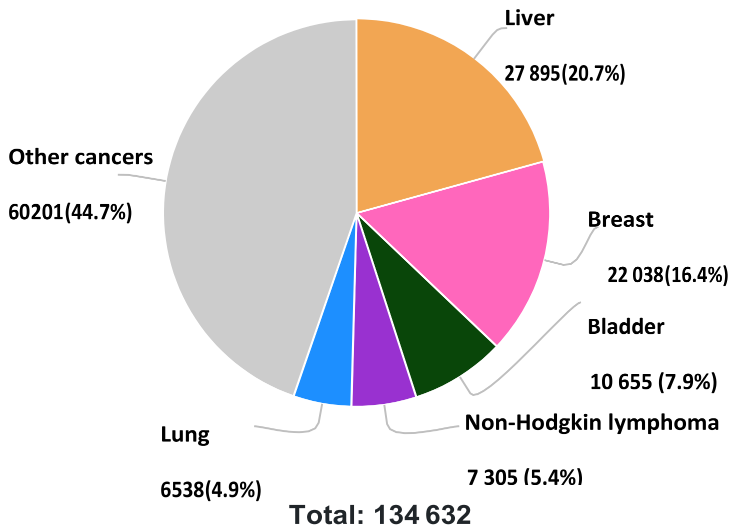


Figure 1: Statistics of cancer cases in Egypt (World Health Organization March,2021).

Diseases of genes cause Cancer:

Inherited or somatic alterations in genes are what make a normal cell ignore growth-controlling signals and form a tumor that eventually leads to the destruction of the organism (Shipitsin *et al.* 2008). Possibly as many as 30% of cancers are caused by smoking, while another 30% are diet related. Carcinogenic chemicals in smoke, food and the environment may cause cancer by inducing gene mutations or interfering with normal cell differentiation. The birth of a cancer (carcinogenesis) can be initiated by a chemical—usually a mutagen but other triggering events, such as exposure to further mutagens, are usually required before a cancer develops (Patrick *et al.* 2013).

2. VEGF receptor

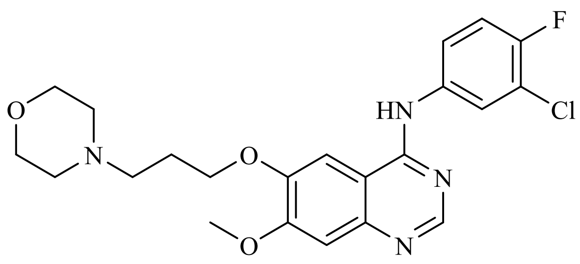
Vascular endothelial growth factor (VEGF) has been identified as the most common regulator of tumor angiogenesis, vascular permeability, endothelial cell activation, proliferation and migration (Ferrara *et al.* 2003). The VEGF family of genes contains at least 7 members, including the viral genome–derived VEGF-E, whereas the VEGFR family of genes has 3 to 4 members depending on the vertebrate species. VEGF-A and its receptors VEGFR-1 and VEGFR-2 play major roles in physiological as well as pathological angiogenesis, including tumor angiogenesis. VEGF-C/D and their receptor VEGFR-3 can regulate angiogenesis at early embryogenesis but mostly function as critical regulators of lymphangiogenesis (Shibuya *et al.* 2011). VEGFR-2 is over-expressed in several malignancies, including hepatocellular carcinoma, breast, colorectal, ovarian and thyroid cancer, melanoma and medulloblastoma (Otrock *et al.* 2007, Gershtein *et al.* 2010, Smith *et al.* 2010).

3. VEGFR inhibitors under clinical assessment

3.1 Gefitinib

Gefitinib (Iressa®) (**1)** was approved by the FDA in 2003 for the treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) (Brehmer *et al.* 2005).

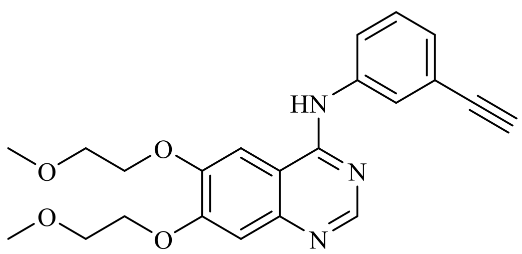
Regarding the effectiveness of Gefitinib within NSCLC patients having an epidermal growth factor receptor (EGFR) mutated status, Gefitinib was found to have elevated efficacy levels in salvage and within NSCLC patients carrying the exon 19 deletion mutation and/or exon 21 Leu858Arg mutation status. (Kanagalingam *et al.* 2023)



(1)

3.2 Erlotinib

In 2004, Erlotinib (Tarceva®) (**2)** was approved by FDA for treating NSCLC. Furthermore, in 2005, FDA approved Erlotinib in combination with Gemcitabine for the treatment of locally advanced, unrespectable, or metastatic pancreatic cancer. Erlotinib acts as a reversible tyrosine kinase inhibitor (Shepherd *et al.* 2005). Although in 2023 , The results of this prospective phase II study will provide evidence on the safety and antitumor activity of combination therapy with Ramucirumab plus Erlotinib in patients with EGFR exon 19 deletion-positive treatment-naïve NSCLC with high PD-L1 expression (Kawachi *et al.* 2023).

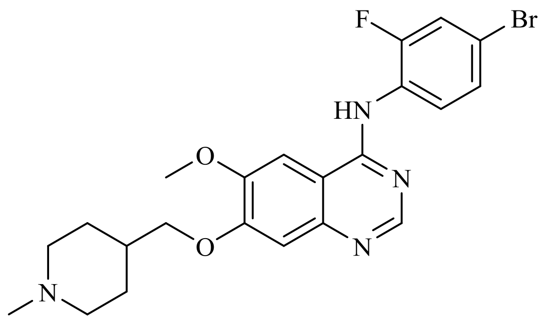


(2)

3.3 Vandetanib

Vandetanib (Caprelsa®) (**3)** inhibits VEGFR-2, EGFR and RET- TS (Morabito *et al.* 2010).

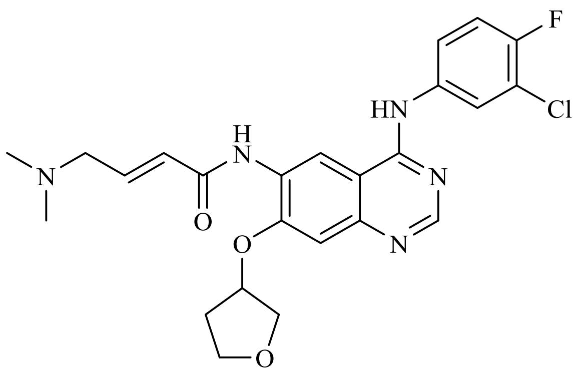
In April 2011, Vandetanib became the first drug to be approved by the FDA for treatment of late-stage (metastatic) medullary thyroid cancer in adult patients who are ineligible for surgery (Commander *et al.* 2011). Genotyping is a predictor of response to Vandetanib and Cabozantinib since patients with an M918T mutation presented with a greater response to Vandetanib in comparison with M918T-negative patients (54.5% vs. 32%) (Martins *et al.* 2023)



(3)

3.4 Afatinib

Afatinib (Gilotrif®) (**4)** was approved by the FDA in 2013 for NSCLC treatment. It acts as an irreversible covalent inhibitor of the receptors tyrosine kinase (RTK) for EGFR and (HER2) (Ismail *et al.* 2016). The results support the notion that Afatinib has an overall advantage over first-generation EGFR-TKIs in the treatment of rare EGFR mutations and is adequate as a first-line treatment preference for NSCLC patients with major uncommon and compound mutation categories among rare EGFR mutations (Jiang *et al.* 2023)



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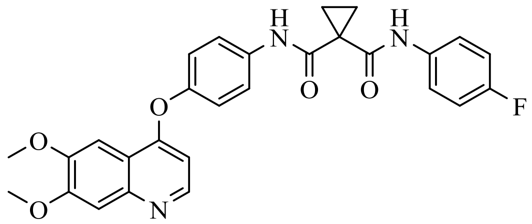
3.5 Cabozantinib

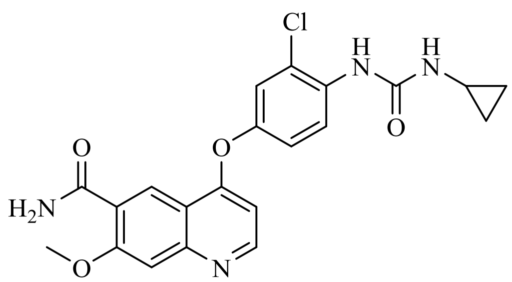
Cabozantinib (**5**) is a multikinase inhibitor that targets VEGFR-2, MET, and RET-TS (Yakes *et al.* 2011). Cabozantinib was granted orphan-drug status by the FDA in 2012 for progressive metastatic medullary thyroid neoplasms (Norman *et al.* 2015). Cabozantinib is associated with a fast and significant volume reduction of brain radionecrosis appearing after SRS and concomitant immunotherapy (Lolli *et al.* 2023)



(5)

3.6 Lenvatinib

Lenvatinib (**6**) is a potent dual inhibitor of VEGFR-2 (IC_{50} = 4.0 nM) and of VEGFR-3 (IC_{50} = 5.2 nM). On February 13, 2015, the U. S. FDA approved Lenvatinib for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (Scott *et al.* 2015). In a proof-of-concept retrospective propensity score-matched study, it was shown that Lenvatinib was associated with significantly improved OS (37.9 vs. 21.3 months; P<0.01), PFS (16.0 vs. 3.0 months; P<0.001) and ORR (73.3% vs. 33.3%; P<0.001). The study also showed that hepatic function deteriorated with repeated TACE (baseline ALBI score from –2.66 to –2.09; P<0.001) but was maintained in the group treated with Lenvatinib (baseline ALBI score from –2.61 to –2.61; P=0.254) (Fujiwara *et al.* 2023)



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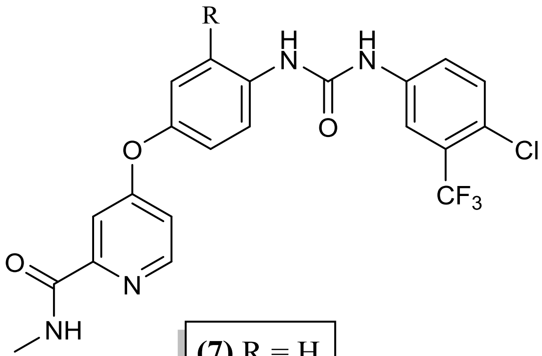
3.7 Sorafenib and Regorafenib

Sorafenib (**7)** (Nexavar®) is a biarylurea multitargeted kinase inhibitor. It inhibits VEGFR-2 and VEGFR-3 (Wilhelm *et al.* 2006). Sorafenib is an oral tyrosine kinase inhibitor with the ability to inhibit tumor cell proliferation and angiogenesis. It has been the first-line option for the group of patients with HCC since it received Food and Drug Administration (FDA) approval in 2008 (Zeng *et al.* 2023) In addition, Regorafenib (**8)** (Stivarga®), a fluoro derivative of Sorafenib developed by Bayer (Wilhelm *et al.* 2004), inhibits angiogenic kinases VEGFR-1/3. Furthermore, it showed anti-proliferative activities on different cancer cell lines (Wilhelm *et al.* 2011). It acts on various tyrosine kinase receptors, including oncogenic, stromal, and angiogenic receptors. Moreover, Regorafenib is highly indicated in the treatment of colorectal cancer, especially in metastatic form. It is also indicated for gastrointestinal stromal tumors (GIST), and hepatocellular carcinoma (Baz *et al.* 2023)

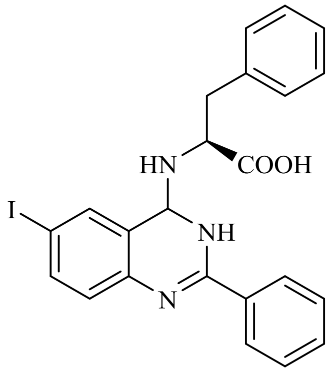
On September 27, 2012, the FDA approved Regorafenib (**8)** for the previously treated metastatic colorectal cancer (mCRC) and then in February 2013, FDA expanded the approved use of Regorafenib to treat patients with advanced gastrointestinal stromal tumors (GIST) (DiGiulio *et al.* 2013).



(7) R = H
(8) R = F

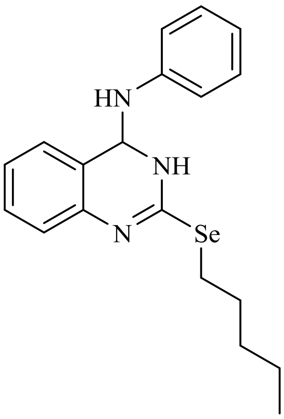
4. VEGFR inhibitors under development

Chandrika *et al* (Chandrika *et al.* 2008), synthesized a series of 2,4,6-tri-substituted quinazoline derivatives. By screening these derivatives for anti-inflammatory and anticancer activities against U937 leukemia cell, it found that compound (**9)** was the most active one.



(9)

In 2012, Moreno *et al*. (Moreno *et al.* 2012), synthesized a series of sulfur and selenium quinazoline and pyrido[2,3-d]pyrimidine compounds and evaluated them for *in vitro* antiproliferative activity against different cell lines cell lines leukemia (CCRF-CEM), colon (HT-29), lung (HTB-54) and breast (MCF-7). The reference drugs were etoposide and cisplatin and the most potent and selective compounds against MCF-7 cells were compounds (**10, 11 and 12)** with GI_{50} values below 10 micromolar.



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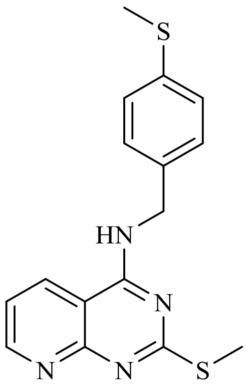

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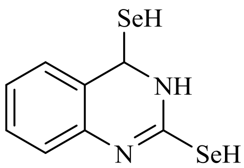
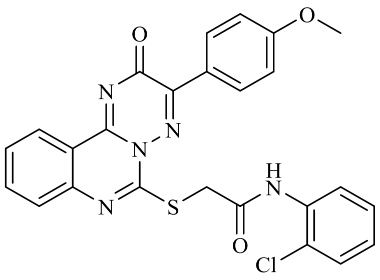


(12)

Kovalenko and co-workers (Kovalenko *et al.* 2013) synthesized a series of *N*-aryl(alkaryl)-2-[(3-R-2-oxo-2*H*-[1,2,4]triazino[2,3-*c*]quinazoline-6-yl)- thio]acetamides. The synthesized compounds were screened *in vitro* for their anti-proliferative activities. Compounds (**13)** and (**14$_{a-c}$**) were the most active members.



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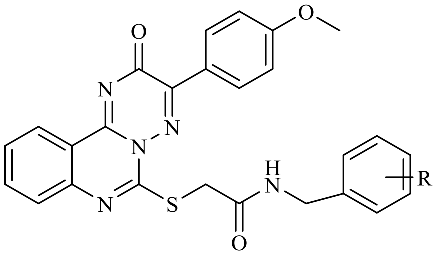
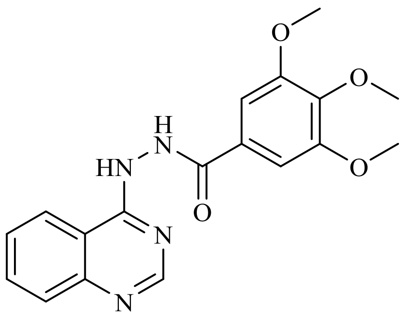


(14a) R = H
(14b) R = 2-OCH_3
(14c) R = 2-F

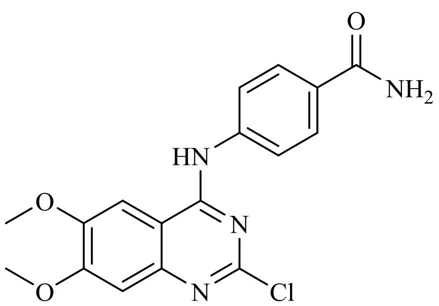
(14a-c)

In 2013, Kovalenko *et al*. synthesized a class of quinazoline derivatives as anticancer agents (Kovalenko *et al.* 2013). The synthesized compounds were screened for antitumor activity against leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancer cell lines. Compound (**15)** was the most active one with GI_{50} in micromolar concentrations. Non-small cell lung cancer (NCI-H522, GI_{50}=0.34), CNS (SF-295, GI_{50}=0.95), ovarian (OVCAR-3, GI_{50}=0.33), prostate (PC-3, GI_{50}=0.56), and breast cancer (MCF7, GI_{50}=0.52), leukemia (K-562, GI_{50}=0.41; SR, GI_{50}=0.29), and melanoma (MDA-MB-435, GI_{50}=0.31).



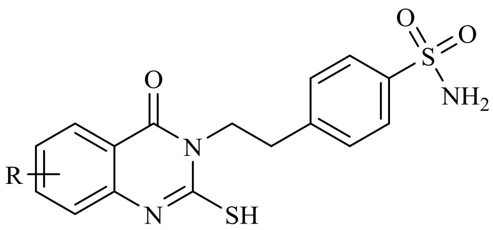
(15)

In 2014, 2-chloro-6,7-dimethoxy-4-substitutedanilinoquinazoline (**16)** elicited potential inhibitory effects on both VEGFR-2 and EGFR with IC_{50} of 1.17 and 0.9 µM respectively (de Castro Barbosa *et al.* 2014).



(16)

Bozdag *et al*. (Bozdag *et al.* 2016) reported synthesis of benzenesulfonamides incorporating 2-mercaptoquinazolin-4-one tails of type (**17)**. These sulfonamides were investigated as inhibitors of subtype II and XII of human carbonic anhydrase (hCA) (a transmembrane, tumor-associated enzyme also involved in glaucoma-genesis). The new sulfonamides were highly effective as hCA II and XII inhibitors.



(17_{a-k})

a) R = 6-F **g) R = 8-CH_3**

b) R = 6-Cl **h) R = 6,8-di-CH_3**

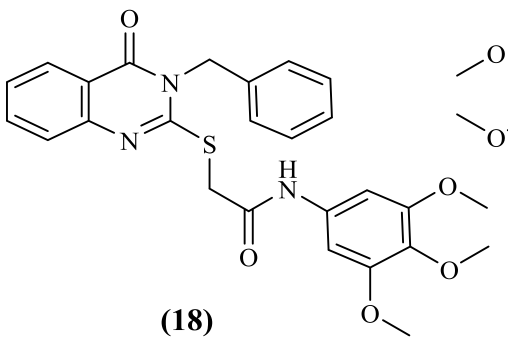
c) R = 7-F **i) R = 8-OCH_3**

d) R = 7-Cl **j) R = 6,7di-OCH_3**

e) R = 6-I **k) R = 7-OCH_3**

f) R = 6-CH_3

Derivatives of 3-benzyl-4(3*H*)-quinazolinones were synthesized and evaluated for their *in vitro* antitumor activities (Al-Suwaidan *et al.* 2016). The results of this study indicated that compounds (**18**, **19** and **20)** possess amazing broad spectrum antitumor activities with mean GI_{50} values nearly about 1.5 - 3.0- fold more potent than that of positive control, 5-FU.



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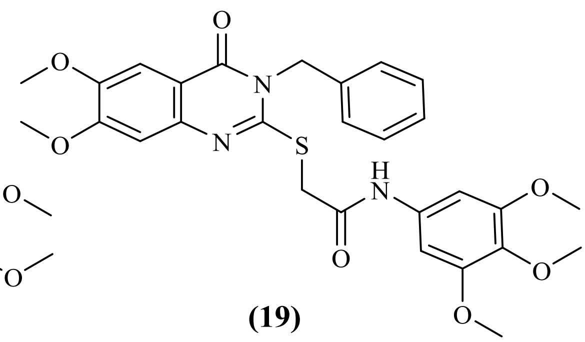

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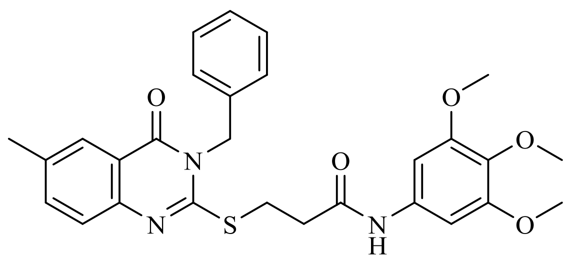
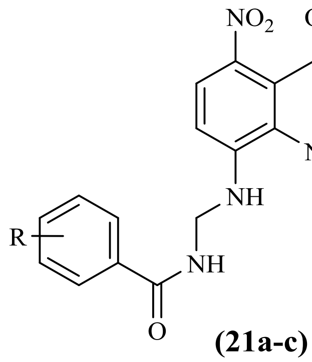


(20)

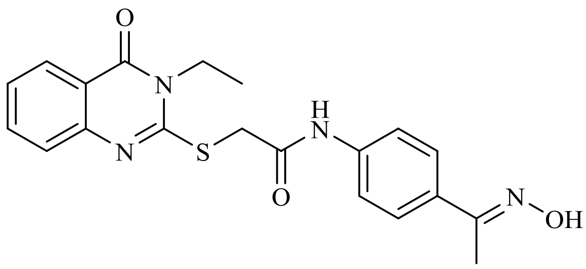
Zhao *et al*. designed and synthesized a class of 5-anilinoquinazoline-8-nitro derivatives that inhibit VEGFR-2 tyrosine kinase. The *in-vitro* cytotoxic activity assay and chick chorioallantois membrane assay showed that these compounds possess anti-tumor activity and anti-angiogenesis (Zhao *et al*. 2019).



(21a-c)

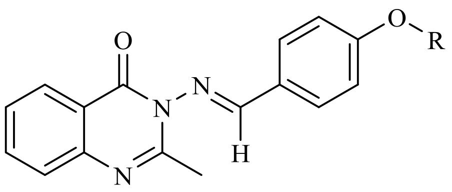
(21a) R = H
(21b) R = 4-OCH_3
(21c) R = 4-F

The synthesized compounds were evaluated for their anti-proliferative activities against a panel of three human cancer cell lines namely; hepatocellular carcinoma (HepG-2), breast cancer (MCF-7) and colorectal carcinoma (HCT-116) using MTT assay. Compound (**22)** has emerged as the most active member against HepG-2 and HCT-116 cells with IC_{50} values of 3.97 ± 0.2, 4.83 ± 0.2 μg/ml, respectively (Mahdy *et al.* 2020).



(22)

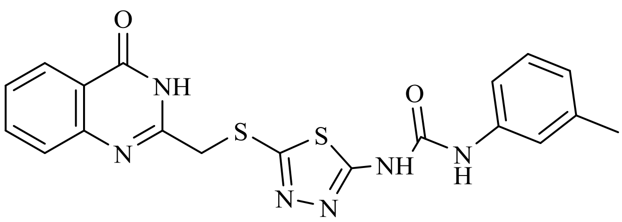
All the synthesized compounds **(23a-h)** were tested *in vitro* for their cytotoxicity against two cancer cell lines, namely human breast cancer (MCF-7), human colon adenocarcinoma (Caco-2) as well as normal human embryonic cells (HEK-293), using the well-established [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) based cell viability assay (Manhas *et al.* 2021).



(23a-h)

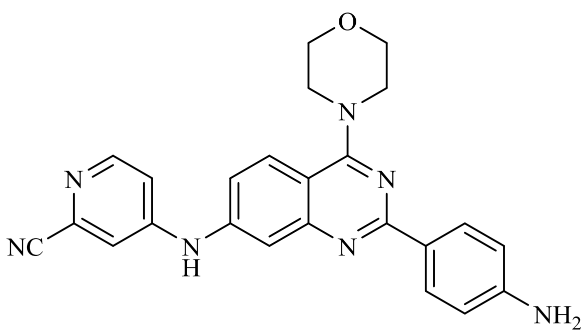
(23a) R = C_2H_5
(23b) R = C_4H_9
(23c) R = C_6H_{13}
(23d) R = $C_5H_{11}Br$
(23e) R = But-3-yn-2-yl
(23f) R = But-2-ynyl
(23g) R = 4-F-benzyl
(23h) R = 2,6 Dichlorobenzyl

A series of quinazolin-4(3*H*)-one based agents containing thiadiazole-urea were designed, synthesized, and biologically evaluated. The proliferation rate of PC3 (prostate cancer) cells was moderately reduced by compound (**24)** (IC_{50} = 17.7 μM) which was comparable with sorafenib (IC_{50} = 17.3 μM) (Faraji *et al.* 2021).



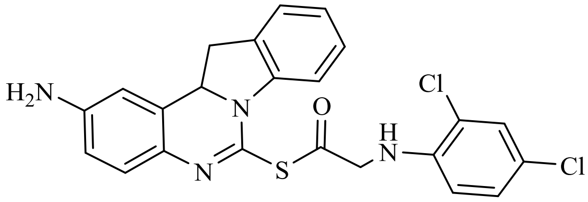
(24)

Some genetics codes had been detected in cancers of the breast, colorectal, liver, and other types of cancer. It has been intensively targeted at this cancer pathway therapies. In 2016, Peng *et al.* synthesized 2-(2-aminopyrimidine-5-yl)-4-morpholino-*N*-(pyridine-3-yl)quinazoline-7-amine (**25)** sequence of PI3K/mTOR inhibitors and anti-cancer activity against seven cancer cell lines were evaluated *in vitro* (Mohamed *et al.* 2021).



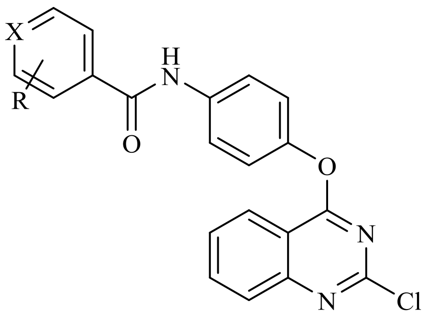
(25)

Benzoimidazoquinazoline (**26**) were synthesized and tested as anticancer lead molecules that modulate the activity of VEGFR, CD34, and microR-122 (Hazem *et al.* 2021).



(26)

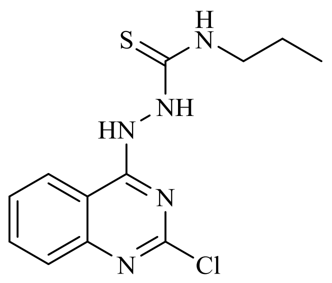
Biological results showed that compounds **27_a** and **27_b** are of particular interest as anticancer agents targeting VEGFR-2 kinase in 2022 Abdallah *et al*. In addition to their considerable inhibition of VEGFR-2, they have shown promising antitumor effects especially against hepatocellular cancer cell line (HepG2) with high degree of selectively (Abdallah *et al.* 2022).



(27a) R = 4-Cl , X = CH
(27b) R = H , X = N

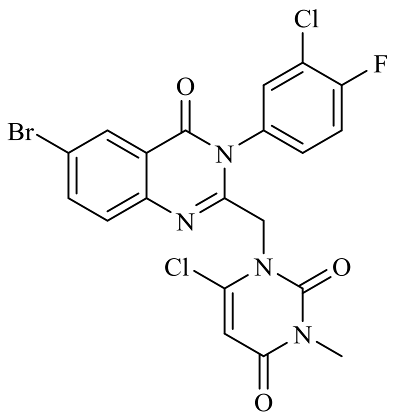
(27a,b)

In 2023, Mabrouk *et al*. synthesized thalidomide analogs. The candidates showed potent *in vitro* anti-proliferative activities against three human cancer cell lines, namely hepatocellular carcinoma (HepG-2), prostate cancer (PC3), and breast cancer (MCF-7). Compound (**28**) was the most potent candidate, with an IC_{50} of 2.03 ± 0.11, 2.51 ± 0.2, and 0.82 ± 0.02 µg/mL compared to 11.26 ± 0.54, 14.58 ± 0.57, and 16.87 ± 0.7 µg/mL for thalidomide against HepG-2, PC3, and MCF-7 cells, respectively (Mabrouk *et al.* 2023).



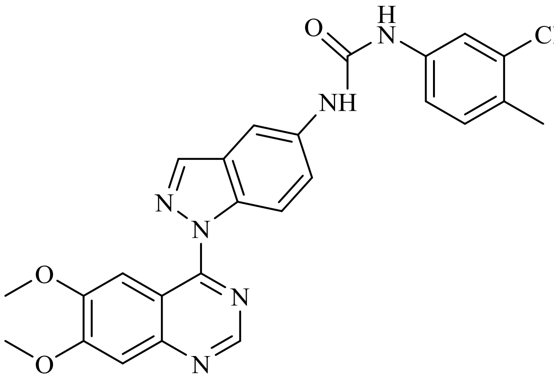
(28)

In 2023, Zari *et al*. examined the antiproliferative activities of some quinazoline derivatives against a panel of three human cancer cell lines (A549, SW-480, and MCF-7) using MTT assay. Among the tested compounds (**29**) showed the highest antiproliferative activities against the tested cell lines. This compound could also induce apoptosis in A549 cell line in a dose dependent manner (Zare *et al.* 2023).



(29)

The molecule (**30**) displayed a potent cytotoxic activity with IC_{50} = 5.4 nM against the VEGFR-2 kinase enzyme in 2023 by Zayed *et al.* It also showed 130% growth inhibition on the full NCI panel of cancer cell lines when exposed to in vitro antiproliferative assay (Zayed *et al*. 2023).



(30)

The antiproliferative assay of the synthesized members by Gaber *et al.* in 2023 against HepG2 and HCT-116 cancer cell lines revealed that compounds **31** showed promising cytotoxicity results with IC_{50} 15.16 µM. Also, the same compound exhibited significant DNA binding affinity with IC_{50} values of 10.25 µM (Gaber *et al.* 2023)

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والعوامل المضادة للسرطان القائمة على مثبطات مستقبلات عامل النمو البطاني الوعائي -٢ الكينازولين

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مثبطات مستقبلات عامل النمو البطاني الوعائي -٢ (VEGFR-2) هي أهداف بيولوجية حاسمة لتطوير أدوية جديدة مضادة للسرطان. يلعب الكينازولين أيضًا دورًا مهمًا كواحد من عناصر البناء للعديد من الأدوية المضادة للسرطان. وهكذا ، تم الانتهاء من مراجعة الأدبيات حول مثبطات VEGFR-2 والأدوية المضادة للسرطان القائمة على الكينازولين. قدمنا مثبطات VEGFR-2 التي تخضع الآن للتقييم السريري ، مثل جيفيتنيب وايرلوتنيب و فاندتنيب و افاتينيب و لينفاتينيب و كابوزانتنيب و سورافنيب وريجورافينيب في دراستنا. بالإضافة إلى ذلك ، تم إدخال مثبطات VEGFR-2 قيد التطوير .

الكلمات المفتاحية : مستقبلات عامل النمو البطاني الوعائي -٢ (VEGFR-2) الكينازولين .عوامل مضادة للسرطان