

AN INSIGHT ON MEDICINAL ATTRIBUTES OF PHTHALAZINE SCAFFOLD, WITH A FOCUS ON THEIR ANTICANCER PROPERTIES AS VEGFR-2 INHIBITORS

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Abstract:

The antitumor properties of synthetic heterocyclic compounds are among the most powerful properties that can be made use in medicinal chemistry. More specifically, their significant cytotoxic effects against many types of human tumor cells, as well as their roles as various kinase inhibitors. In recent years, Phthalazine derivatives, have frequently attracted the interest of medicinal chemistry researchers due to their promising anticancer properties. The present study is a review of the latest advances in Phthalazine derivative-related research, with a focus on their anticancer activities as VEGFR-2 inhibitors.

Keywords: Anticancer, Phthalazine, VEGFR-2 inhibitors, Kinase, Angiogenesis.

1. Introduction:

Cancer is the rapid creation of abnormal cells that grow beyond their usual limits, which can then invade adjoining parts of the body and spread to other organs, this process is referred to as metastasizing (C. C. Harris, 1993). Cells reproduce by a series of well arranged events where cellular macromolecular contents are duplicated, followed by division into two daughter cells. Dividing cells pass through four distinct phases during the cell cycle (Cheeseman & Desai, 2008). The G₁-phase where cells increase in size and prepare to copy their DNA. Then, The S-phase during which DNA is replicated (S for DNA synthesis). The G₂-phase during which cells further grow. M-phase when chromosomes separate, and cells divide (M for mitosis). After one cycle, the daughter cells can continue to enter a new cycle, enter G₀ phase or become terminally differentiated (Sui et al., 2023). Cancer arises from the transformation of normal cells into malignant cells in a multistage process that generally progresses from a pre-cancerous lesion to a malignant tumour (Colditz, Sellers, & Trapido, 2006). Current cancer therapies include four major types: surgery, radiotherapy immunotherapy, and chemotherapy. Chemotherapy can be used alone, but is usually used in combined therapy modalities, along with surgery and/or radiotherapy, to achieve and maintain remission. The aim of chemotherapy is to completely eradicate disease. Tumors nevertheless commonly relapse, and such relapses may occur locally or at a distance (metastasis) from the primary tumor site (Schirrmacher, 2019).

2. Chemotherapeutic agents

The history of chemotherapy traces back to medical observations in World War 1 where soldiers who were exposed to chemical warfare (Sulphur Mustard), suffered from lowering of their white blood cells, especially lymphocytes. Since the discovery of the toxic action of nitrogen mustards on blood cells, many chemotherapeutic agents have been discovered by screening the cytotoxic potency of a large number compounds *in vitro* or *in vivo* models (Abotaleb et al., 2018).

They are generally classified according to their mechanism of action into:

2.1. Alkylating agents, this type of drugs are cell cycle-nonspecific agents, they cause cell death by cross-linking DNA strands, which result in inhibition of DNA, RNA and protein synthesis. It includes, nitrogen Mustards (Cyclophosphamide), Alkyl Sulphonates (Busulfan), Nitrosureas (Carmustine), and Platinum Agents (Cisplatin) (Warwick, 1963).

2.2. Antimetabolites, they have structural similarities to natural existing substances, such as Vitamins, nucleosides or amino acids. They mainly comprise folic acid antagonists, pyrimidine analogues and purine analogues. They act by competing with natural substrates for the active site on receptors. Some antimetabolites are incorporated directly into DNA or RNA, resulting in inhibition of DNA, RNA and protein synthesis (Kaye, 1998). It includes, Purine analogues (Azathioprine), pyrimidine analogues (5-Fluorouracil, **5-FU**), and antifolate (Methotrexate, **MTX**) (Alam et al., 2018).

2.3. Topoisomerase Inhibitors, there are two classes in topoisomerase Inhibitors: Topoisomerase I inhibitors and Topoisomerase II inhibitors. They are involved in all DNA synthesis, such as DNA replication, transcription, recombination, and chromosome condensation. Inhibition of topoisomerase results in induction of DNA strand breaks and inhibition of cell proliferation. This class of drugs are cell cycle-specific and prevent cells from entering mitosis (Ewesuedo & Ratain, 1997). It includes, topoisomerase I inhibitor (Topotecan), Topoisomerase II inhibitors (Doxorubicin) (Gelderblom & Sparreboom, 2007).

2.4. Cytotoxic antibiotics, most of them are derived from bacteria and fungi. They have various mechanisms of action. They affect the function and synthesis of nucleic acids in various ways. It includes Mitomycin C, Actinomycin D, Bleomycin and Anthracyclines ("Cytotoxic Antibiotics," 2012).

2.5. Anti-microtubule agents, Vinca alkaloids and Taxoids are the two main groups of anti-microtubule agents. Although both types of agents cause microtubule dysfunction, resulting in blocking of cell division, they have opposite mechanisms of action. The Vinca alkaloids prevent the polymerization of the microtubules, whereas Taxoids prevent microtubule depolymerization. Examples for this class includes: - Vincristine and Paclitaxel, **PTX** (Florian & Mitchison, 2016).

2.6. Hormone therapy, the principle hormonal treatments available are Selective Estrogen Receptor Modulators (**SERMS**) and Selective Androgen Receptor Modulators (**SARMS**). Their basic principle is to prevent the hormone signals that contribute to cancer cell growth. Tamoxifen (Nolvadex®) was the first **SERM** to be widely used. **SERMS** mechanism of action lies in their binding to the estrogen receptor and thereby inducing a conformational change. Its major drawback is that it has an estrogenic effect in endometrial tissue. The next generation of **SERMS** such as Raloxifene (Evista®) do not display this estrogenic effect. **SARMS** such as flutamide (Eulexin®) work by binding preferentially to androgen receptors on the cancer cell thereby blocking the binding of Testosterone and Dihydroxytestosterone

(**DHT**). Other important hormone-based therapies include Luteinising Hormone-Releasing Hormone (**LHRH**) agonists which are used in the treatment of prostate cancer. These include peptides such as Leuprolide, Goserelin, and Buserelin (Johnston & Cheung, 2018).

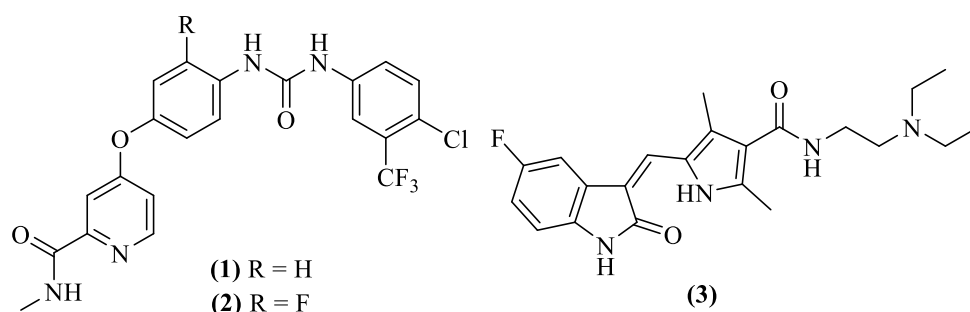
2.7. Protein kinases inhibitors, Protein kinases (PKs) catalyze phosphorylation of different cellular substrates. Phosphorylation in turn regulates various cellular functions. Normally, their activity is stringently regulated. However, under pathological conditions, PKs can be deregulated, leading to alterations in the phosphorylation, resulting in uncontrolled cell division, apoptosis inhibition and consequently tumor. Various cancers and other diseases are known to be caused or accompanied by deregulation of the phosphorylation. Inhibition of PKs has been shown to be a promising therapeutic strategy for treatment of cancer (Shchemelinin, Sefc, & Necas, 2006). Tyrosine kinases are primarily classified as: i) receptor tyrosine kinase (RTK) (e.g., EGFR, VEGFR, FGFR and ILGFR). They are not only cell surface transmembrane receptors but are also enzymes having kinase activity. So that, they are

activated by ligand binding to the extracellular domain (Hunter, 1995; Schlessinger, 2000). ii) Non-receptor tyrosine kinase (NRTK) (e.g., SRC, ABL, FAK and Janus kinase). They are cytoplasmic proteins, exhibiting considerable structural variability (Schenk & Snaar-Jagalska, 1999). VEGFR-2 is the major regulator of VEGF-driven responses in endothelial cells, including permeability, proliferation, invasion, and migration. Moreover, it is considered to be a crucial signal transducer in both physiologic and pathologic angiogenesis. VEGFR-2 is over-expressed in several malignancies, including hepatocellular carcinoma, breast, colorectal, ovarian and thyroid cancer, melanoma and medulloblastoma (Gershtein, Dubova, Shchegolev, & Kushkinskii, 2010; Otrrock, Makarem, & Shamseddine, 2007; Smith et al., 2010). Thence, the discovery of small molecule inhibitors that block the autophosphorylation of VEGFR-2 arises as a prime target for discovering therapies for many human malignancies.

3. VEGFR Inhibitors, Targeting VEGF receptors represents one approach that has enjoyed a great therapeutic success. To date, seven drugs targeting VEGFRs have been approved for clinical use (Liu et al., 2022).

3.1. Biarylurea derivatives, Sorafenib **1** (Nexavar[®]) is a biarylurea multitargeted kinase inhibitor. It inhibits VEGFR-2 and VEGFR-3 (S. Wilhelm et al., 2006). Sorafenib was approved for the treatment of advanced renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) (Woo & Heo, 2012). In addition, regorafenib **2** (Stivarga[®]), a fluoro derivative of sorafenib developed by Bayer (S. Wilhelm, Dumas, Ladouceur, Lynch, & Scott, 2004), inhibits angiogenic kinases VEGFR-1/3. Furthermore, it showed anti-proliferative activities on different cancer cell lines (S. M. Wilhelm et al., 2011). In September 2012, the FDA approved regorafenib **2** 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) (Wu et al., 2022).

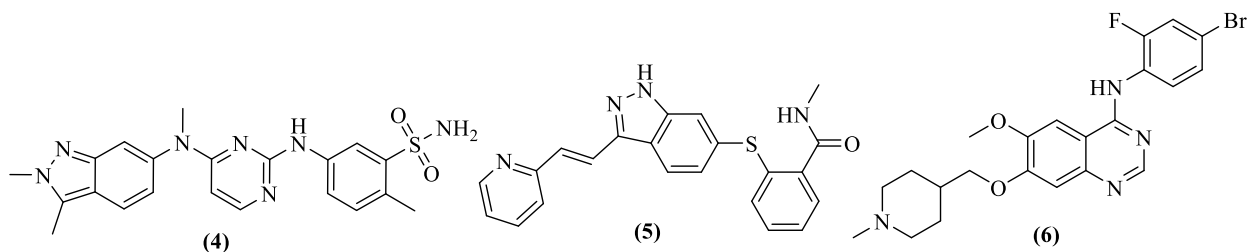
3.2. Indol-2-one derivative, Sunitinib **3** (Sutent[®]) is a multikinase inhibitor targeting VEGFR-2, PDGFR β and other kinases, including FLT3, which has been shown to be involved in acute leukemia (Schenone, Brullo, & Botta, 2008). Sunitinib was approved in 2006 by the FDA for the treatment of RCC and of GIST (Guislain et al., 2015).



3.3. Indazole derivatives, Pazopanib **4** (Votrient[®]) is a potent VEGFR inhibitor (P. A. Harris et al., 2008). It was approved by the FDA for RCC and soft tissue sarcoma (Bukowski, Yasothan, & Kirkpatrick, 2010). Furthermore, axitinib **5** (Inlyta[®]), developed by Pfizer as a multikinase inhibitor. It is active on VEGFR-1/3 (Ho &

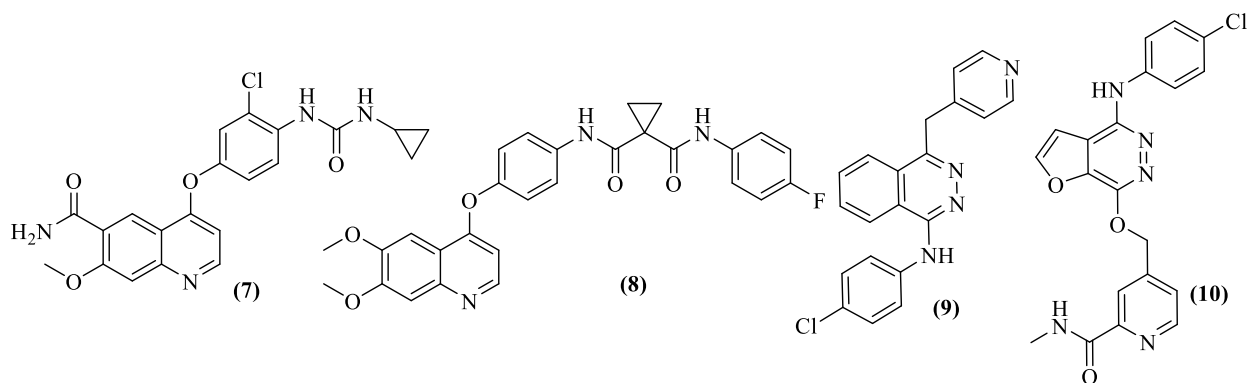
Jonasch, 2011). On January 2012, the U.S. FDA approved axitinib for use in patients with RCC that had failed to respond to a previous treatment (Shang, Hou, Meng, Shi, & Cui, 2021).

3.4. Anilinoquinazoline derivative, Vandetanib **6** (Caprelsa[®]) 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, Whiteside, & Perry, 2011).

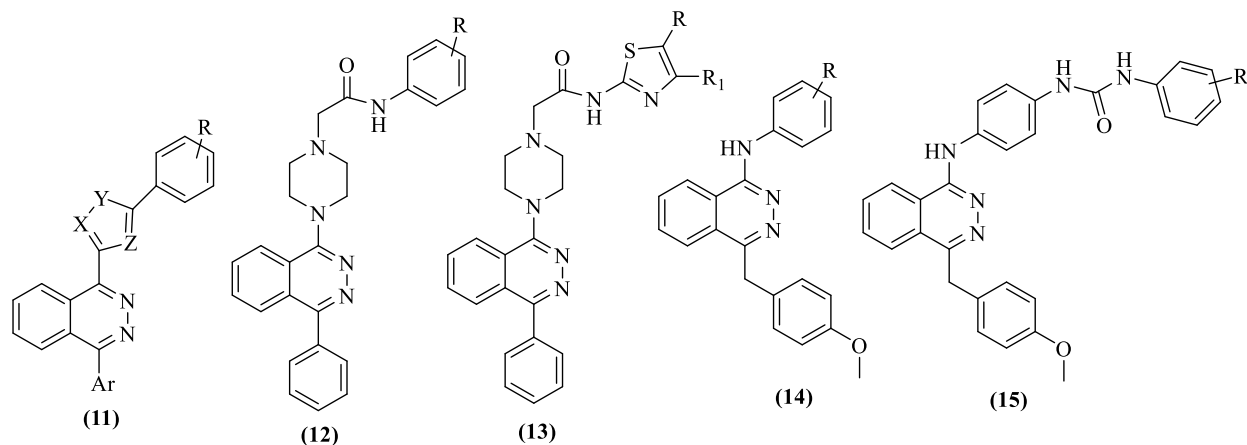


3.5. Quinoline derivatives, Lenvatinib **7** is a potent dual inhibitor of VEGFR-2 ($IC_{50} = 4.0$ nM) and of VEGFR-3 ($IC_{50} = 5.2$ nM). In February 2015, the U. S. FDA approved lenvatinib for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. Cabozantinib **8** 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, 2015).

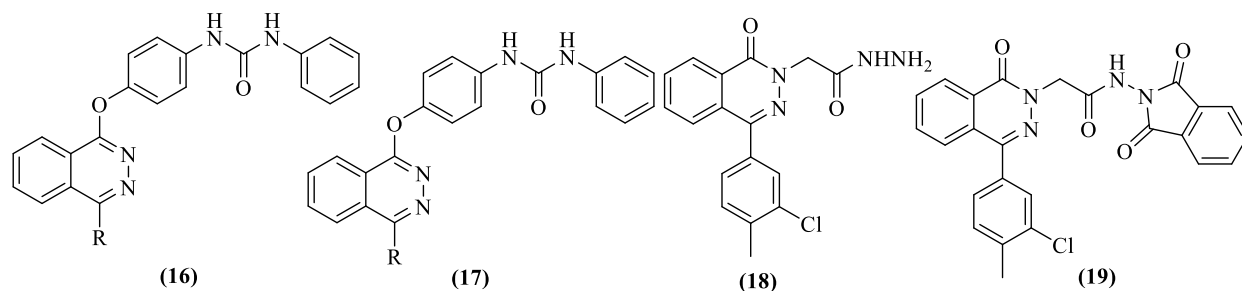
3.6. Phthalazine derivatives, Vatalanib **9** is being developed by Bayer Schering and Novartis. It inhibits all known VEGF receptors, as well as platelet-derived growth factor receptor-beta and c-kit but is most selective for VEGFR-2. Vatalanib was one of the earliest VEGFR2 inhibitors used for wet AMD. Vatalanib was reported that oral vatalanib was being evaluated for safety and efficacy in patients with subfoveal CNV at doses of 500 and 100 mg/day (Zaib & Khan, 2020). Also, **telatinib 10**, the furopyridazine derivative, emerged as a potent and orally available inhibitor of VEGFR-2, VEGFR-3 with IC_{50} s 6 and 4 nM, respectively. It is currently in clinical trials for gastric and colorectal cancer (SalwaElmeligie, Aboul-Magd, Lasheen, & Abouzid, 2018).



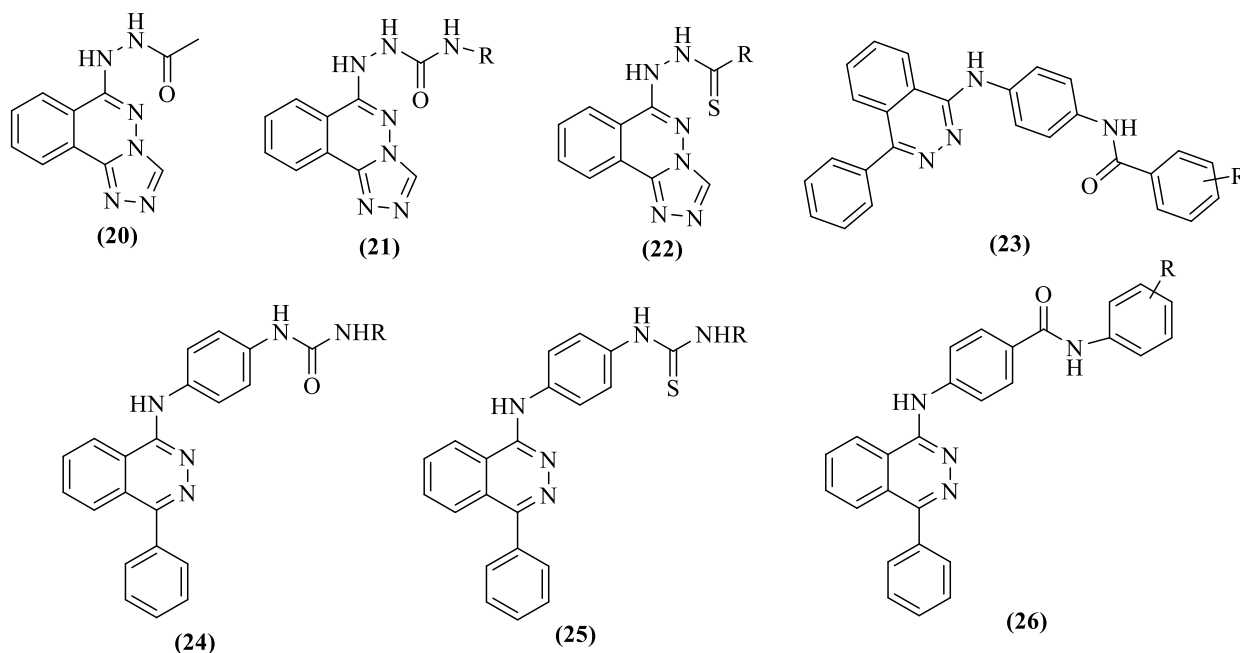
4. Phthalazine derivatives as VEGFR inhibitor, during the last two decades there is a growing interest in the synthesis of several phthalazine derivatives for the treatment of cancer as potent inhibitors of VEGFR-2. In 2006 Alexander S. Kiselyov synthesized series of novel arylphthalazines as potent inhibitors of both VEGFR-II and VEGFR-I receptors **11** (Kiselyov, Semenova, Semenov, & Piatnitski, 2006). In 2015, Abou-Seri *et al.*, synthesized anovel series of phthalazine derivatives based on 1-piperazinyl-4-arylphthalazine scaffold which show high activity against VEGFR-2 **12** and **13** (Abou-Seri, Eldehna, Ali, & Abou El Ella, 2016). In 2016, Eldehna *et al.*, synthesized anilinophthalazine derivatives showed promising activity in the VEGFR-2 kinase inhibition assay with IC_{50} ranged between 0.64 and 5.76 μM **14** and **15** (Eldehna *et al.*, 2016).



In **2016** Salwa *et al.*, synthesized phthalazine-based derivatives linked to abiarylamide or biarylurea tail to position 1 of the phthalazine core via an amino or ether linkage have been designed and synthesized as VEGFR-2 kinase inhibitors **16** and **17** (Elmeligie, 2016). In 2017 El-Hashash *et al.*, synthesized new series of Phthalazine derivatives with anti-tumor activity 18 and 19 (El-Hashash *et al.*, 2017).

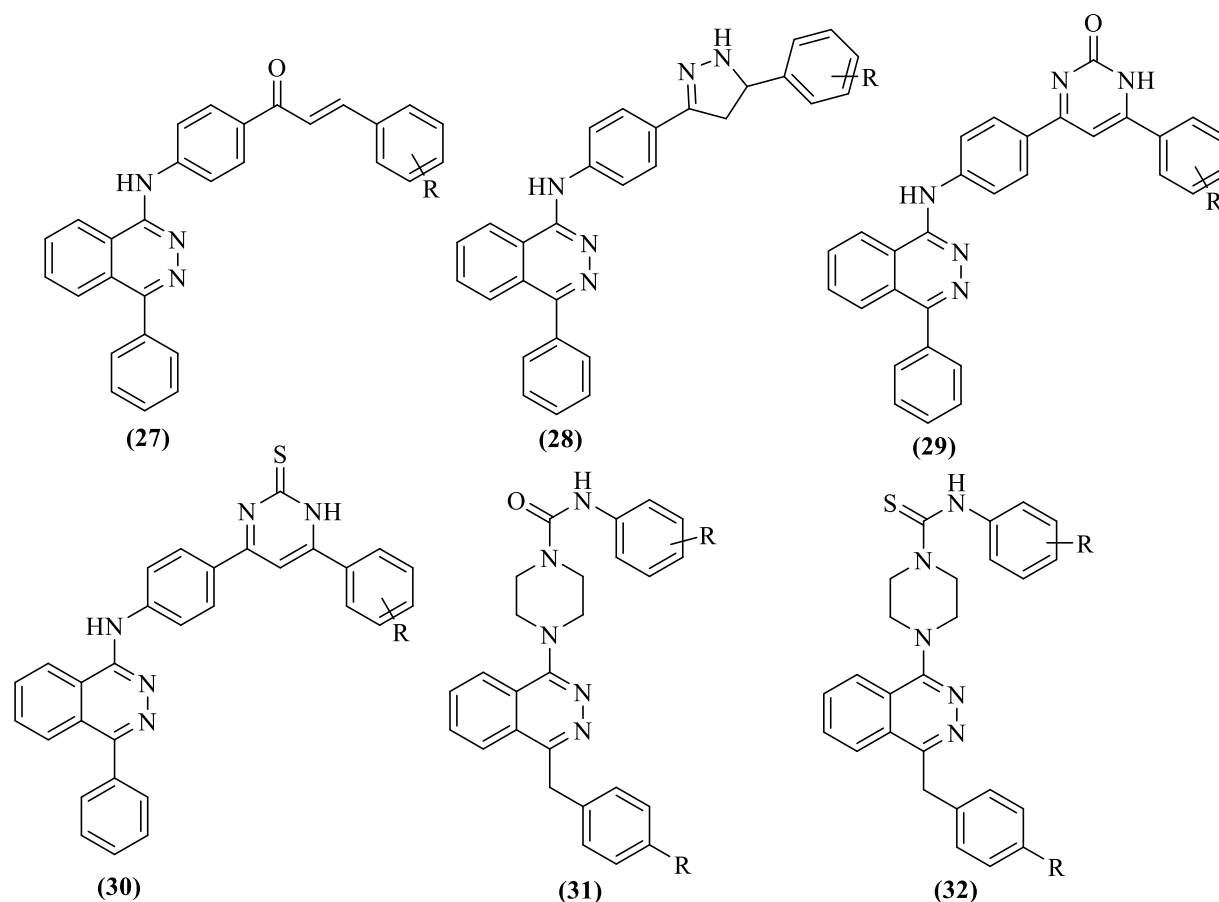


In 2017, El-Helby *et al*, synthesized novel series of phthalazine derivatives and evaluated for their anticancer activity against two human tumor cell lines, HCT-116 human colon adenocarcinoma and MCF-7 breast cancer cells, targeting the VEGFR-2 enzyme, **20-22** (El-Helby *et al.*, 2017). In 2020, El-Adl *et al*, synthesized new N-substituted-4-phenylphthalazin-1-amine derivatives against HepG2, HCT-116, and MCF-7 cells as VEGFR-2 inhibitors. The results of the cytotoxicity investigation indicated that HCT-116 and MCF-7 were the most sensitive cell lines to the influence of the newly synthesized derivatives **23-26** (El-Adl, Ibrahim, Khedr, Abulkhair, & Eissa, 2021).



In 2021, Khedr *et al*, designed compounds with a new linker was inserted in the form of fragments with verified VEGFR-2 inhibitory potential, including an α,β -unsaturated ketonic fragment, pyrazole, and pyrimidine. Also, new distal hydrophobic moieties were attached to these linkers that are expected to increase the hydrophobic interaction with VEGFR-2, **27-30** (Khedr, Ibrahim, Eissa, Abulkhair, & El-Adl, 2021). In 2022, Akl *et al*, synthesized novel series of 1-piperazinyl-4-benzylphthalazine derivatives as promising anticancer agents with CDK1 inhibitory activity. The anti-proliferative activity of these agents was first screened on a panel of 11 cell lines representing 5

cancers (pancreas, melanoma, leukemia, colon and breast), and then confirmed on two CDK1-overexpressing PDAC cell lines (MDA-PATC53 and PL45 cells) **31** and **32** (Akl et al., 2022).



5. Conclusion:

Phthalazine scaffold was considered as an important class of bicyclic *N*-heterocycles, have received considerable attention due to their beneficial biological and pharmacological activities. phthalazines play a significant role in medicinal chemistry and have emerged as a pharmacophore. The phthalazine ring is a crucial pharmacophoric scaffold present in the core structures of numerous anticancer molecules with potent activity against hepatocellular carcinoma, colon cancer, and breast cancer. Many studies were reported in the synthesis of several phthalazine derivatives as promising anticancer agents as powerful VEGFR-2 inhibitors. The first anilinophthalazine derivative to be identified as a strong inhibitor of VEGFR-2 was vatalanib. According to this review, phthalazine is a major biological active pharmacophore in medicinal chemistry, as well as a new lead scaffold for safe and effective drugs.

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نظرة ثاقبة على السمات الطبية لسقالة الفثالازين ، مع التركيز على خصائصها المضادة للسرطان كمثبطات لعامل النمو البطاني الوعائي ٢.

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الملخص:

تعد الخصائص المضادة للأورام للمركبات الحلقية غير المتجانسة الاصطناعية من بين أقوى الخصائص التي يمكن استخدامها في الكيمياء الطبية. وبشكل أكثر تحديداً ، آثارها السامة للخلايا الكبيرة ضد العديد من أنواع الخلايا السرطانية البشرية ، وكذلك أدوارها كمثبطات كيناز مختلفة. في السنوات الأخيرة ، جذبت مشتقات الفثالازين في كثير من الأحيان اهتمام الباحثين في الكيمياء الطبية بسبب خصائصها الواعدة المضادة للسرطان. الدراسة الحالية هي مراجعة لأحدث التطورات في الأبحاث المتعلقة بمشتقات الفثالازين ، مع التركيز على كيفية تصنيع هذه المشتقات وعلى أنشطتها المضادة للسرطان كمثبطات لعامل النمو البطاني الوعائي ٢.

الكلمات المفتاحية : مضاد للسرطان ، فثالازين ، مثبطات عامل النمو البطاني الوعائي ٢ ، كيناز ، تولد الأوعية.