ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org
ISSN: 0970-020 X
CODEN: OJCHEG
2025, Vol. 41, No.(6):
Pg. 1920-1941

"Targeting Angiogenesis": A Comprehensive Review of VEGFRInhibitors

AISWARYA G* and KALPANA DIVEKAR

College of Pharmaceutical Sciences. Dayananda Sagar University,
Bangalore-560111, India.
*Corresponding author E-mail: aiswaryagurunidhi@gmail.com

http://dx.doi.org/10.13005/ojc/410608

(Received: April 22, 2025; Accepted: November 23, 2025)

ABSTRACT

The process of formation of fresh blood vessels is identified as angiogenesis, it plays a significant part in a variety of pathological circumstances, as well as tumor, ocular disorders, and inflammatory diseases. Vascular Endothelial Growth Factor Receptor (VEGFR) blockers have appeared as a pivotal class of therapeutics, primarily in the realm of oncology owing to their potent anti-angiogenic properties. Synthesis of VEGFR inhibitor or Vascular Endothelial Growth Factor Receptor inhibitors has been at the forefront of anti-angiogenic drug development, instrumental in the therapeutic landscape of oncology as well as other vascular-related diseases. This comprehensive review focuses on various heterocyclic derivatives as VEGFR inhibitors and provides insights into their structural activity relationships (SAR), highlighting the importance of specific structural elements that enhance binding affinity and efficacy. Our discussion extends to the therapeutic applications of VEGFR inhibitors in cancer treatment, emphasizing the outcomes of clinical trials and real-world utilization. This review provides an in-depth analysis of the chemical strategies and methodologies employed in the synthesis of various VEGFR inhibitors.

Keywords: VEGFR inhibitors, Anti-angiogenic agents, Oncology therapeutics, Structure-activity relationship (SAR).

INTRODUCTION

Consistent to the WHO, tumor was a most important reason of demise universal, accountable for 10 million deaths, the majority frequent cancers in the year integrated breast cancer (2.26 million cases), lung cancer (2.21 million cases), colorectal cancer (1.93 million cases), prostate cancer (1.41 million cases), stomach cancer (1.09 million cases) and non-melanoma skin cancer (1.20 million cases)[1].

Cancer is a condition where the uninhibited augmentation and increase of certain organisms happen within the corpse. Under typical conditions, human cells undergo cell division, creating new cells to replace old or damaged ones[2].

However, this organized process can sometimes malfunction, leading to the proliferation of abnormal cells. Such growth can result in tumors, which might be benign (non-cancerous) or malignant (cancerous). One can view cancer

as a genetic disease, arising from mutations in the genes responsible for regulating cellular growth and multiplication. Tumors are not just masses of cancer cells. They have a complex "microenvironment" consisting of resistant cells, fibroblasts, blood vessels, and various molecules. Cancer growth and progression are heavily influenced by the tumor's microenvironment. Within this setting, elements such as Platelet-derived growth factor (PDGF) vascular, endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), are secreted not just by the cancer cells themselves, but also by cells that infiltrate the cancer, like lymphocytes and macrophages. These factors are pivotal in activating pro-antigenic signaling pathways. These pathways, in turn, fuel the processes of tumor angiogenesis, expansion, incursion, and the potential for metastasis. Angiogenesis, vascularization, is a key player in cancer's development. The rationale is simple: without a dedicated blood supply, tumors can't grow beyond a certain size or metastasize to distant sites. Recognizing this, researchers have engineered drugs known as angiogenesis inhibitors. These drugs, often referred to as antiangiogenic agents, aim to halt or retard cancer growth by depriving tumors of the blood they need to flourish. Thus, blocking angiogenesis is considered as one of the foremost effective and unique strategies in cancer treatment[3].

Process of angiogenesis

The procedure of angiogenesis is proscribed by many factors, the main responsible factor is the VEGFs, There are four VEGF isoforms they are VEGF-A, B, C, D and placental growth factor (PIGF). Members of the VEGFs family act together with various Vascular Endothelial Growth Factor Receptors VEGFR-1/Flt-1, VEGFR2/KDR and VEGFR-3/Flt-44. VEGFR-1 and VEGFR-2 were initially recognized on endothelial cells. VEGF and its receptors has a major role to play not only in physiological angiogenesis but they have a major role in pathological angiogenesis also[5]. The organic impact of Vascular Endothelial Growth Factor is conveyed through two receptor tyrosine kinases: VEGFR-1 and VEGFR-2. Among these receptors, research indicates that VEGFR-2 primarily drives endothelial cell mitogenesis, angiogenesis, and alterations in microvascular permeability[6].

VEGF is also recognized as VPF, which binds to VEG aspect receptor, activating intracellular tyrosine kinase and initiate a cascade of signaling events essential for vasculogenesis and angiogenesis[7].

When ligand binds, the VEGFRs generate intracellular signals through different mediators. in case of VEGF-2, the mediators generated are, mitogen-activated kinases, phosphotidylinositol-3 kinase (PI3K)/Akt, the non-receptor tyrosine kinase Src, as well as phospholipase C gamma (PLCγ)/ protein kinase C (PKCγ), they endorse angiogenesis, vascular permeability, vascular homeostasis and lymphangiogenesis[8].

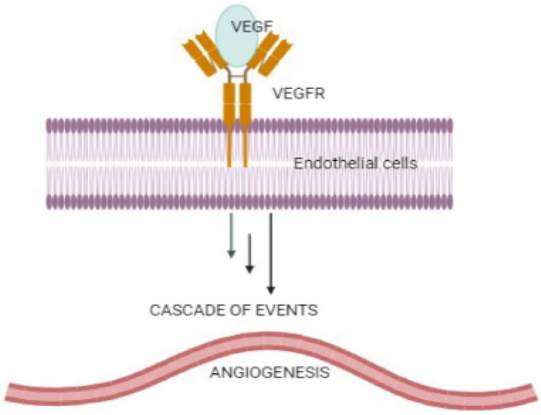


Fig. 1. Angiogenesis

Anti-angiogenic agents as antitumor drugs

Angiogenesis is a multifaceted event chain. While vascular endothelial growth factors (VEGFs) target either blood or lymphatic vessels based on their specific affinities to VEGF receptors 1, 2, and 3, it's notable that VEGFR-2 is present on both blood and lymphatic endothelium. Therefore, any growth factors stimulating VEGFR-2 have the potential to support the expansion of both blood (angiogenesis) and lymphatic vessels (lymphangiogenesis). Therefore, VEGFR-2 is widely acknowledged as the main therapeutic target for developing treatments related to tumor associated angiogenesis[9].

Structural features of VEGFR inhibitors

FDA approved VEGFR-2 receptor inhibitors have some pharmacophoric characteristics which are necessary for the inhibition of VEGF. There are four main structural features for these drugs as follows.

(i) “In order to shape an important hydrogen bond with the backbone NH of Cys917 remains, the key amino acid residue in the

catalytic ATP-binding domain, the majority of inhibitors have a flat hetero aromatic ring system with at least one H-bond acceptor (N atom is preferred, followed by the O atom).

(ii) A middle spacer, or aryl ring, those reside in the linker area among the enzyme's DFG area and ATP-binding area.

(iii) A functional group (such as urea or amide) that functions as a pharmacophore and has both donor and acceptor H-bonds to connect with 2 critical remainders (Asp1044 and Glu883) in the Diabetic Foot Gangrene (Asp-Phe-Gly) motif, a tripeptide series that is necessary in the lively kinase area. While the CO motif forms another hydrogen bond with Asp1044, the urea or amide moiety's NH motifs often form two hydrogen connections with Glu883.

(IV) When the phenylalanine residue of the DFG loop spins out of its lipophilic sack, defining the Diabetic Foot Gangrene-out or immobile conformation, the blockers incurable hydrophobic moiety takes up residence in the recently created allosteric hydrophobic sack. Consequently, this allosteric binding area is typically where hydrophobic interactions are achieved. Additionally, examination of the X-ray structures of several blockers attached to Vascular Endothelial Growth Factor Receptor–2 verified that there is enough room for different substituents surrounding the incurable hetero perfumed ring"[10].

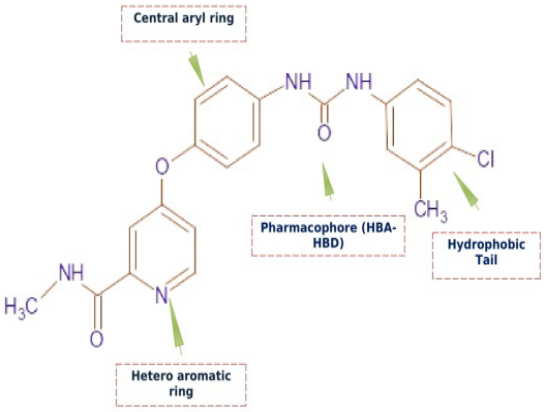
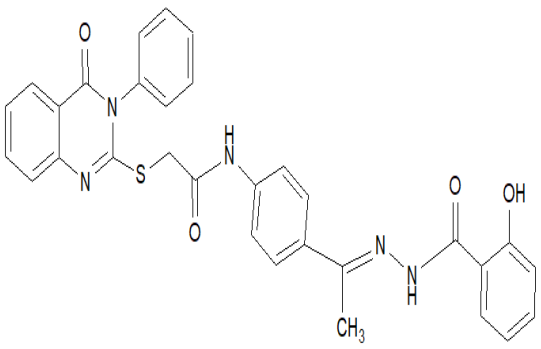


Fig. 2. The essential structural necessities of reported VEGFR-2 inhibitors

Inhibitors of VEGFR offer significant potential in cancer treatment. Numerous derivatives are currently under investigation and in clinical trials. Some FDA-approved compounds have demonstrated encouraging results in treating cancer. This article aim to provide a thorough review of various heterocyclic derivatives as VEGFR inhibitors.

Quinazoline derivatives

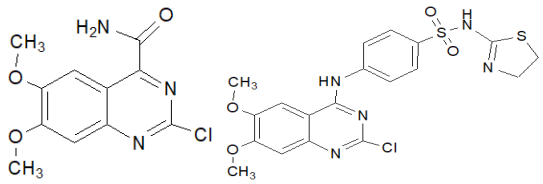
Quinazoline derivatives have been found to have various therapeutic effects, including anticancer properties. Some quinazoline derivatives act as inhibitors for VEGFR-2. The general structure of quinazoline is a six-membered ring (benzene) fused with another ring containing two nitrogen atoms. Modifications to this structure can lead to a variety of derivatives, and these modifications can decide the activity of the compound as a VEGFR-2 inhibitor. This makes the quinazoline backbone a versatile template for the growth of innovative remedial representatives. A sequence of quinazolinone derivatives were developed by Ibrahim. H. Eissa *et al.,* and tested for their VEGFR-2 inhibitory action and found that out of the 16 derivatives compound 1 has demonstrated significant cytotoxic action opposed to HepG-2(hepatoblastoma cell line), MCF-7(human adenocarcinoma cells.), and HCT-116 cell lines (human colorectal carcinoma cell line). Compound 1 had shown lower IC_{50} values (3.74, 5.00, and 6.77 µM) against the three cell lines compared to doxorubicin (8.28, 9.63, 7.67 µM) and sorafenib (7.31, 9.40, 7.21 µM), implying that it had been more potent than these reference drugs in terms of cytotoxic activity. Quinazoline derivative (1) has demonstrated inhibitory activity opposed to Vascular Endothelial Growth Factor Receptor-2. The IC_{50} assessment of Quinazoline derivative (1) for VEGFR-2 inhibition had been 0.340 µM, again lower than that of sorafenib (0.588 µM), indicating superior potency[11].



(1)

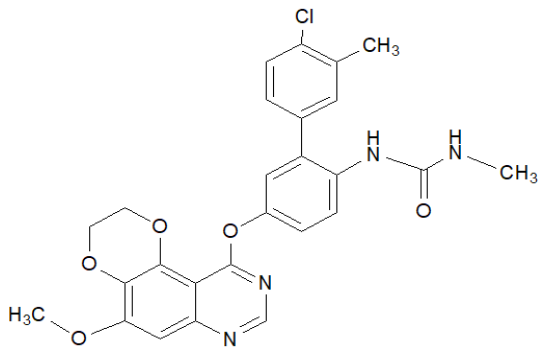
Maria Letícia de Castro Barbosa *et al.,* designed novel quinazoline derived as double inhibitors of the VEGFR-2 and EGFR pathways. The biological data indicated that these derivatives show promising potential as dual inhibitors, with

Quinazoline derivative (2) standing out due to its heightened potency towards both VEGFR-2 and EGFR, as evaluated to the prototype Quinazoline derivative 2a. Structure-Activity Relationship (SAR) studies, beside with docking studies, helped identify the pharmacophoric groups responsible for the interactions with both kinases. The studies also highlighted the significance of a hydrogen bond giver at the para location of the aniline group for interaction with the preserved Glu (Glutamic acid) and Asp (Aspartic acid) amino acids in the binding sites of both Vascular Endothelial Growth Factor Receptor-2 and Epidermal Growth Factor Receptor[12].



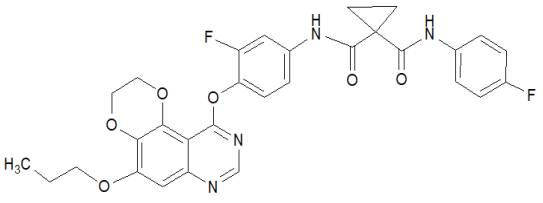
(2) (2a)

Haoru Fan and colleagues designed 12 quinazoline compounds and tested them as potential inhibitors of VEGFR-2. Among these, Quinazoline derivative 3 displayed strong inhibitory activity against both Vascular Endothelial Growth Factor Receptor-2 and HUVECs, boasting impressively low IC_{50} values. Specifically, its IC_{50} value against Vascular Endothelial Growth Factor Receptor-2 was 2 nM, and it also demonstrated significant inhibition of HUVECs proliferation with an IC_{50} of 1.2 nM. In addition, when Quinazoline derivative 3's antitumor properties were evaluated in animal models, it exhibited a remarkable tumor growth inhibition (TGI) rate of 133.0% after just six days of treatment. Such a high TGI percentage indicates that not only was the tumor growth halted, but the tumor size also decreased, marking compound 3 as a potent anticancer agent[13].

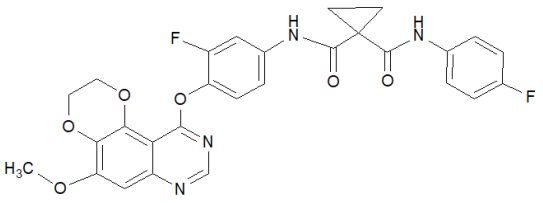


(3)

Dengshuai Wei *et al.,* designed and synthesized a sequence of [1,4]dioxino[2,3-f] quinazoline derivatives in an attempt to create reversible and noncovalent 9, c-Met (mesenchymal-epithelial transition factor) and VEGFR-2 dual inhibitors. The enzyme assay results indicate that most of these newly synthesized compounds can inhibit together c-Met and Vascular Endothelial Growth Factor Receptor-2, with IC_{50} values in the nanomolar choice. The Quinazoline derivative 4 and 4a, in particular, showed promising results. The *in vitro* cell proliferation assay further strengthened these findings. Specifically, compound 4a demonstrated significant anti-tumor activity on a hepatocellular carcinoma (MHCC97H cells) xenograft mouse method[14].

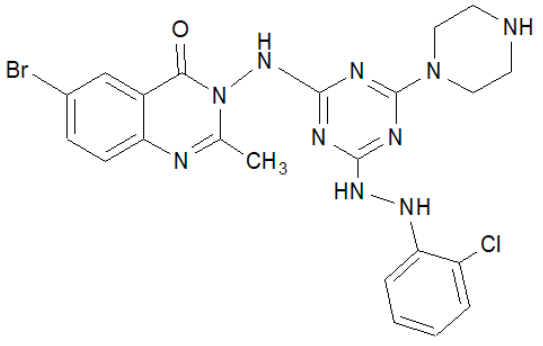


(4)

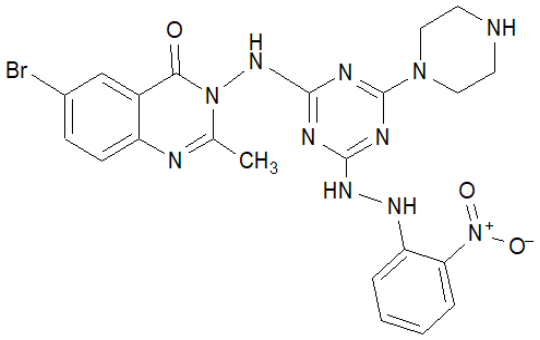


(5)

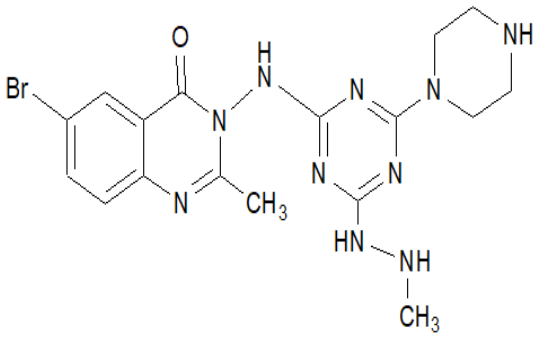
Prateek Pathak *et al.,* designed A sequence of quinazoline clubbe 1,3,5-triazine derivatives were created and assessed for their *in vitro* anticancer activity against HL-60 (human promyelocytic leukemiacell), HepG2 (human Hepatocellular carcinoma cell), HeLa (human cervical cancer), MCF-7 (human breast cancer cell), and one usual cell line HFF (human foreskin fibroblasts). In the series of compounds, among the synthesized derivatives molecules 5, 5a, and 5b exhibit important activity. These consequences were backed by a docking study on VGFR2[15].



(5)



(5a)



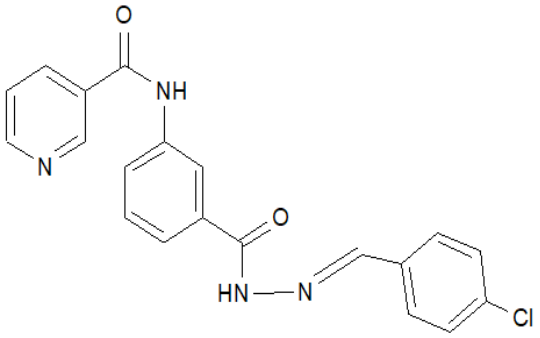
(5b)

Nicotinamide derivatives

Nicotinamide, also identified as niacinamide, is a structure of vitamin B3 that has been studied in various contexts for its potential benefits in medicine. When it comes to anticancer therapy, nicotinamide has gained interest due to its diverse cellular effects that might be beneficial in both cancer prevention and treatment. Here are some of the ways in which nicotinamide has been investigated in anticancer therapy.

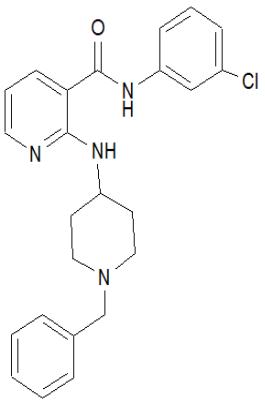
Ultraviolet radiation from the sun can increase the threat for different skin cancers. Nicotinamide has been shown to enhance DNA mend and reduce UV-induced immunosuppression in the skin. Nicotinamide have been exposed to inhibit the movement of an enzyme called poly (ADP-ribose) polymerase (PARP). PARP acts a part in DNA restore and its inhibition can make some cancer cells, particularly those with certain genetic mutations like BRCA mutations, more susceptible to death[16].

Eslam B. Elkaeed *et al.,* designed four nicotinamide-supported derivatives as antiangiogenic VEGFR-2 inhibitors the derivatives were designed possessing essential pharmacophoric features to attach properly with the Vascular Endothelial Growth Factor Receptor-2 active pocket. Out of the synthesized compounds 6 showed the most promising results in cytotoxic studies. It demonstrated potent cytotoxicity against HCT-116 (a colorectal cancer cell line) and HepG-2 (a liver cancer cell line), as shown by low IC_{50} values. Also, it displayed an important inhibitory effect on Vascular Endothelial Growth Factor Receptor-2, with an IC_{50} of 60.83 Nm[17].

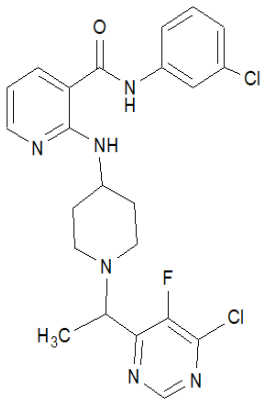


(6)

Hye-Eun Choi *et al.,* synthesized five nicotinamide derivatives, out of which piperidine substituted derivative (7) showed potent inhibitory effects on VEGF-induced HUVECs. It demonstrated a dose-reliant inhibition of Vascular Endothelial Growth Factor-induced migration, propagation, and capillary-like tube structure in human umbilical vein endothelial cells, as well as vessels developing from mouse aortic rings. The compound mechanism was originated to involve the suppression of Vascular Endothelial Growth Factor -encouraged phosphorylation of the VEGR2 and the activations of AKT and eNOS[18].



(7)

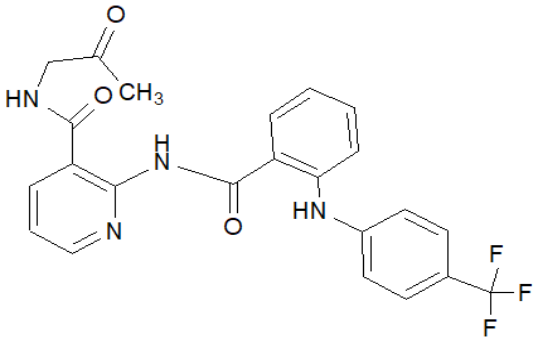


(8)

As a continuous study Hye-Eun Choi *et al.,* synthesized another Pyrimidine nicotinamide

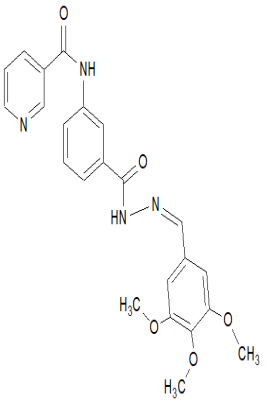
derivative (8) which is potent and extensively repressed human umbilical vein endothelial cells propagation, relocation, tube formation, and micro vessel expansion in an attention variety of 0.01–0.001 μM[19].

Min Peng *et al.,* designed and synthesized nicotinamide unit containing diamide derivatives. The created compounds were assessed for their cytotoxic effects and found that they exhibited excellent to reasonable cytotoxic effects on lung cancer cell lines. From the series of synthesized derivative 9, exhibited the extremely possible inhibitory actions opposed to NCI-H460 cell line with the IC_{50} values of 4.07±1.30 μg/mL[20].

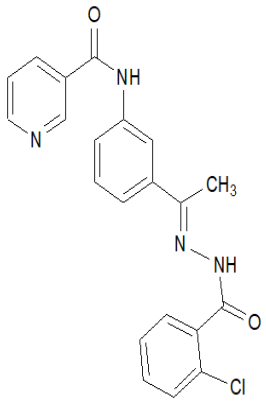


(9)

Reda G. Yousef *et al.,* designed four nicotiamide derivatives and reviewed for their Anti-cancer and immunomodulatory action as apoptosis inducers and potential VEGFR-2 inhibitors. These synthesized derivatives showed encouraging antiproliferative impacts on HTC lines HepG2 and HCT-116, coupled with notable VEGFR-2 inhibitory activity. Specifically, Compounds 10 and 10a demonstrated cytotoxic effects on HCT-116, boasting IC_{50} values of 15.7 and 15.4, while on HepG2, their IC_{50} values were 15.5 and 9.8 mM respectively. These were assessed in comparison to sorafenib, which had IC_{50} values of 9.30 and 7.40mM. All the derivatives consistently displayed commendable Vascular Endothelial Growth Factor Receptor-2 inhibitory activities with IC_{50} values in the sub-micromolar series. Taking Compound 10a as a prime example, deeper mechanistic studies revealed its ability to halt the cell cycle at the G2-M and G0-G1 stages, amplifying apoptosis in HCT-116 cells by five times in relation to the control. Additionally, both derivatives 7 and 10 diminished the concentrations of immunomodulatory proteins TNF-a by 84.5% and 81.6% and IL-6 by 60.9% and 88.4% correspondingly. This was benchmarked against dexamethasone, which showed reductions of 82.4% and 93.1%[21].



(10)

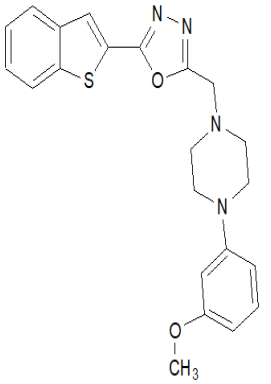


(10a)

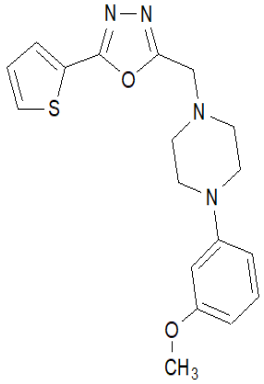
Oxadiazole derivatives

Oxadiazoles are 5 membered rings with a composition of 2 carbons, 2 nitrogens, and one oxygen atom, appearing in various regioisomeric structures. These motifs are commonly found in drug-like compounds and are typically utilized as bioisosteric substitutes for ester and amide groups. Several oxadiazole derivatives were produced and assessed for their anticancer potential age opposed to various types of cancer cell lines. Oxadiazole derivatives might exert their anticancer effects through various mechanisms. Some may obstruct with the cell cycle, induce apoptosis, inhibit angiogenesis, or target specific enzymes involved in cancer cell proliferation.

Zühal Kilic-kurt developed new oxadiazole derivatives, and evaluated the molecular properties and bioactivity. Each of the created compounds adhered to Lipinski's rules, suggesting they have potential as drug candidates. In assessments of drug-likeness, compounds 11 and 11a achieved the top scores of 0.31 and 0.33, correspondingly. The compounds' most significant predicted bioactivity pointed to their role as kinase inhibitors. Moreover, molecular docking studies suggested that these compounds have the potential to create hydrogen bonds with the lively location of Vascular Endothelial Growth Factor Receptor-2 kinase, implying they might inhibit Vascular Endothelial Growth Factor Receptor-2 kinase action *in vitro*[22].

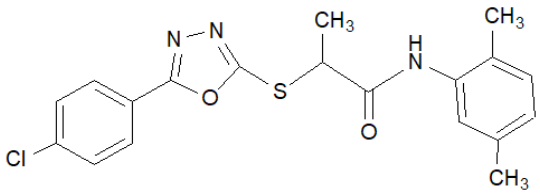


(11)

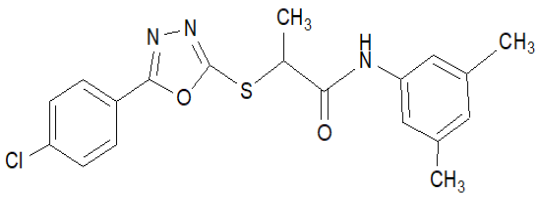


(11a)

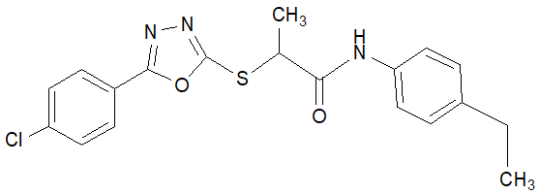
Muhammad Sajjad Bilal *et al.,* carried out a study where they screened fourteen anti-inflammatory 1,3,4 oxadiazoles derivatives, previously reported by their individual team,for their potential anti-cancer efficacy, targeting VEGFR2 and EGFR's tyrosine kinase domain.Most tyrosine kinase inhibitors sanctioned by the FDA have been described as simultaneously inhibiting EGFR and VEGFR 2. So in their study they aimed to identify a potent, specific VEGFR 2 inhibitor to combat renal cancer. They employed a comprehensive virtual screening approach which included density functional theory to assess molecules constancy/reactivity, ligand docking for binding similarity estimation, structure-activity relationship scrutiny, compound active reproductions for protein-molecular multifaceted constancy, and absorption, distribution, metabolism, and excretion–toxicity (ADMET) profiling for pharmacokinetic analysis. DFT indicated that derivatives 12,12a, and 12b were both stable and highly reactive. Molecular docking of these optimized structures revealed that 12, 12a, and 12b had the strongest affinity for VEGFR 2, with binding energy values of -46.32, -48.89, and -45.01 kJ/mol respectively[23].



(12)

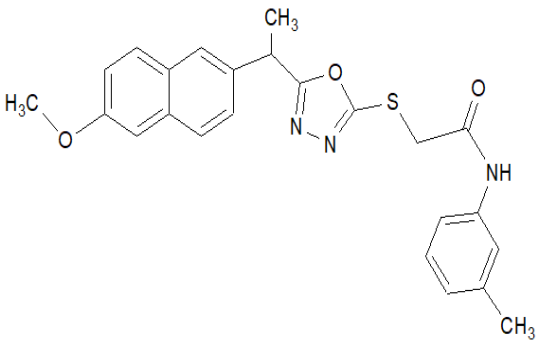


(12a)



(12b)

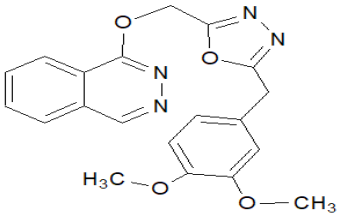
Mohamed Hagrasa and his team formulated and produced 1,3,4-oxadiazole-naphthalene hybrid compounds as VEGFR-2 inhibitors. They assessed the antiproliferative effects of fourteen such synthesized molecules adjacent to 2 human tumor cell types: HepG-2 and MCF-7. Out of those, six compounds displayed notable cytotoxic effects with values ranging from 8.4 to 10.4 mM, comparable to sorafenib, which had IC_{50} values of 10.8 mM for MCF-7 and 10.2 mM for HepG2 cells. These compounds also demonstrated VEGFR-2 inhibitory capabilities, Among them, compound 13 stood out as the most potent, leading to a marked rise in apoptosis (22.86% compared to the control's 0.51%) and predominantly halted the expansion of HepG2 cells at the Pre-G1 stage. Moreover, compound 13 significantly amplified the caspase-3 level by 5.61 times. Docking analyses indicated that these newly formulated compounds bind similarly to sorafenib at the VEGFR-2 active site[24].



(13)

Fang Qiao *et al.,* designed a series of 4-alkoxyquinazoline derivatives with a 1,3,4-oxadiazole. Their potential inhibitory effects were examined on MCF-7, A549, and Hela cell lines of these, compound 14 showcased the highest inhibitory activity with IC_{50} values of 0.23 μM, 0.38 μM, as well as 0.32 μM for MCF-7, A549, and Hela correspondingly. This was benchmarked against the known control, tivozanib. A preliminary analysis of structure-activity relationships (SARs) and molecular

modeling gave deeper understanding into the enzyme-ligand interplay. Observing the binding pose of compound 14 in the active site revealed it was anchored through interactions with Lys868, Cys919, His1026, and Asp1026[25].



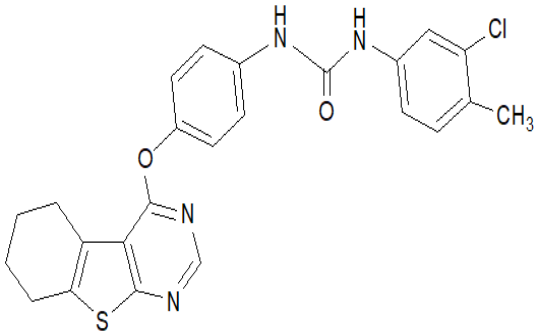
(14)

Pyrimidine derivatives

Heterocyclic aromatic molecules with 2 nitrogen particles at places 1 and 3 of the six-membered rings, such as pyridine and benzene, are known as pyrimidines. Because they make up a significant class of both natural and nonnatural compounds, many of which have beneficial biological activity and clinical uses, heterocycles with a pyrimidine moiety are of great attention.

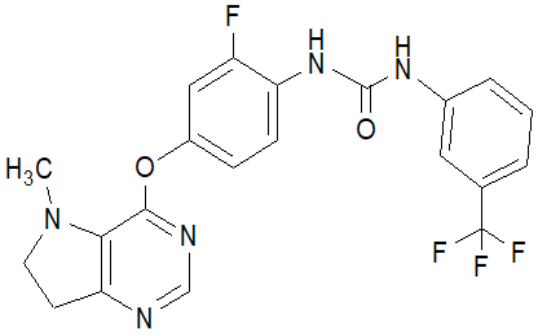
In recent years, huge integers of innovative pyrimidine molecules have been formed for their anticancer properties.

Furo[2,3-d] pyrimidine and thieno[2,3-d] pyrimidine are two sequence of pyrimidine-based derivatives that were created by Marwa Aziz *et al.,* and connected to moreover biarylamide otherwise diaryl urea by an NH or ether linker. They tested their anti-proliferative and VEGFR-2 inhibitory properties beside the NCI 60 cell line panel in vitro. At 10 Mm concentration, the majority of the diaryl urea-supported derivatives attached to moreover of the merged pyrimidine scaffolds showed high-quality to powerful vascular endothelial growth factor receptor-2 inhibition; in general, derivatives with an ether linkage showed higher VEGFR-2 inhibition than their aniline counterparts. With IC_{50} values in the nanomolar range, seven urea-based compounds demonstrated strong dose-related VEGFR-2 inhibitory action. By the use of the air linker at location 4, the thieno[2,3-d] pyrimidine imitative compound 15 containing 1-(3-chloro-4-methylphenyl)-3-phenyl urea demonstrated a very strong nanomolar reserve of VEGFR-2 kinase (IC_{50}21 nM)[26].



(15)

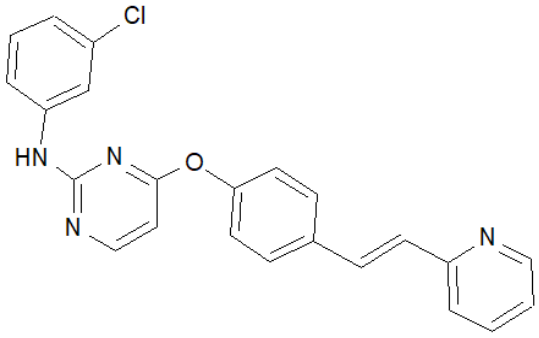
A number of pyrrolo[3,2-d] pyrimidine derived were amalgamated by Yuya Oguro *et al.,* who then assessed their potential as type-II inhibitors of VEGFR-2 kinase. Integrating a diphenylurea segment at the C4-position of the pyrrolo[3,2-d] pyrimidine structure using an oxygen linker resulted in effective inhibitors of VEGFR2 kinase. Additionally, introducing a meta-substitution of the urea terminal benzene ring and substitution with a small lipophilic group at the 2-position of the central benzene ring enhanced HUVEC (Human Umbilical Vein Endothelial Cells) inhibitory activity. Out of the manufactured compounds compound number 16 was extremely potent[27].



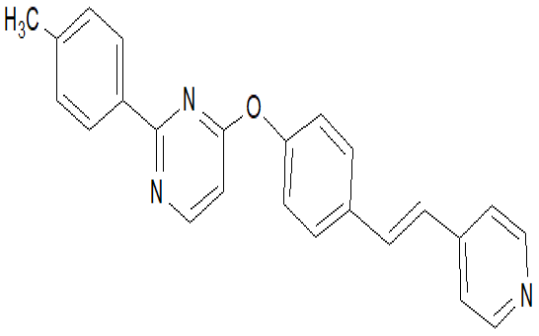
(16)

Wuji Sun and co-workers intended as well as synthesized a succession of novel pyrimidine-based derivatives as vascular endothelial growth factor receptor-2 inhibitors. In comparison to Pazopanib, the majority of derivatives demonstrated superior inhibitory potencies on HepG2 and A549 cell lines, according to biological evaluation. Between the derivatives examined, compound number 17 (with IC_{50} values of 9.19 and 14.59 μM), compound number 17a (IC_{50} values of 9.95 and 18.21 μM), and compound number 17b (IC_{50} values of 13.17 and 11.94 μM) showcased remarkable cellular potency on both cell types, outperforming Pazopanib. To understand more structure-activity relationships

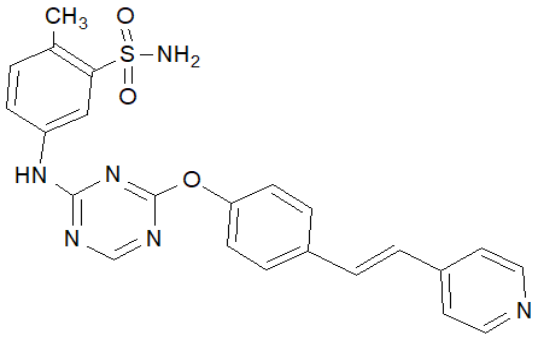
(SARs) of these pyrimidine-based derivatives were conducted. The consequences indicated that compound number 17(ΔG = -10.54 kcal/mol, Ki = 0.018 µM), compound number 17a (ΔG = -10.60 kcal/mol and Ki = 0.016 µM), and compound number 17b (ΔG = -10.37 kcal/mol, Ki = 0.025 µM) had superior binding efficiencies when evaluated to Pazopanib, reliable with their imposing cellular activity[28].



(17)

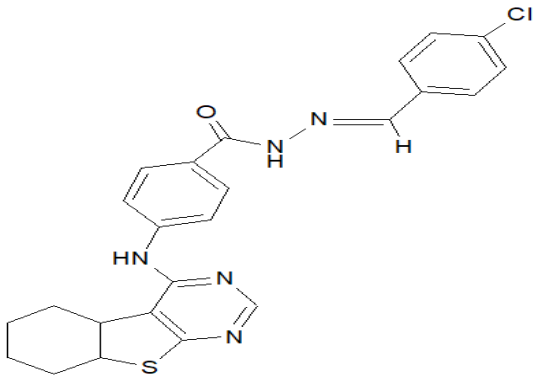


(17a)



(17b)

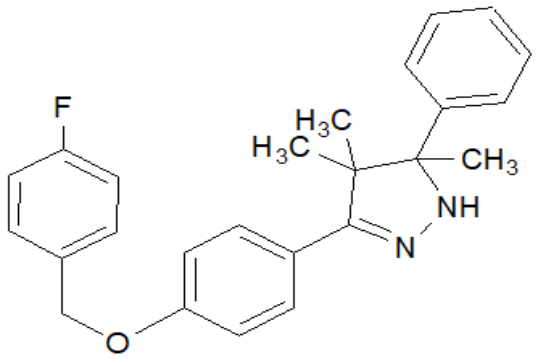
New eighteen thieno[2,3-d]pyrimidine derivatives with aliphatic and fragrant hydrophobic tails connected to the thieno pyrimidine nucleus with various spacers were developed and synthesized by Souad A. El-Metwally *et al.,* In comparison to the reference chemical, sorafenib, various of synthesized molecules demonstrated extra effective cell growth inhibition against hepatocellular carcinoma (HepG2) and colorectal carcinoma (HCT116) cell lines. With an IC_{50} value of 0.23±0.03 similar to that of the reference compound, sorafenib (IC_{50} values of 0.23±0.04) Compound 18 had the highest potency. By forecasting the potential binding connections between the objective drugs and the vascular endothelial growth factor receptor-2 lively locations, docking experiments validated these findings[29].



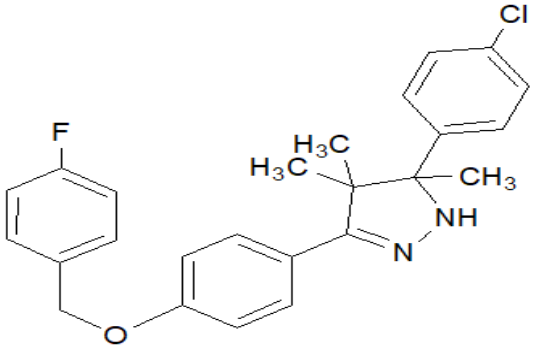
(18)

Pyrazoline and pyrazole derivatives

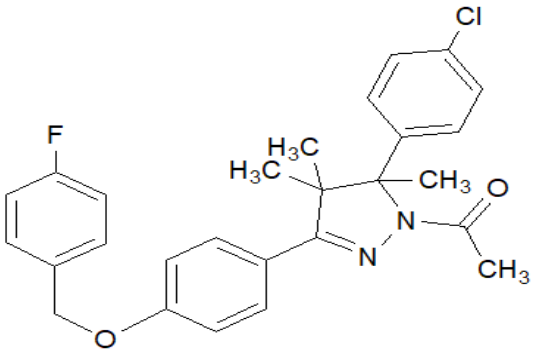
A novel set of pyrazolines was created and examined by Omkulthom M. Alkamaly etal for their potential cytotoxic effects *in vitro* on PC-3, HepG2, and MDA-MB-231 cancer cell lines. Many of these compounds displayed promising anticancer properties. Notably, derivatives number 19, 19a, 19b, and 19c exhibited strong and versatile antitumor activity across the assessed cancer cells. Furthermore, these compounds displayed a preference for targeting cancer cells over normal WI-38 cells, suggesting a favorable safety profile. The inhibitory efficiency of these compounds on various RTKs was also explored. The findings pinpointed EGFR and VEGFR vulnerability to the compounds under scrutiny, especially 19b and 19c. These two showed IC_{50} values between 0.21 and 0.23 µM, outperforming the benchmark, erlotinib[30].



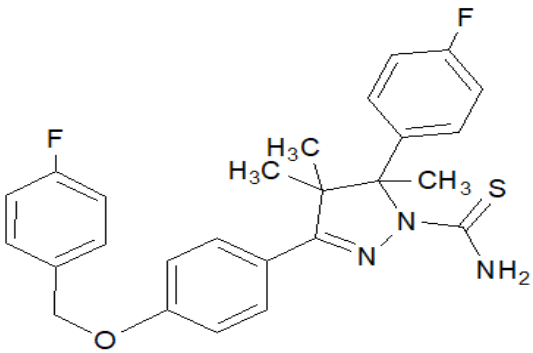
(19)



(19a)



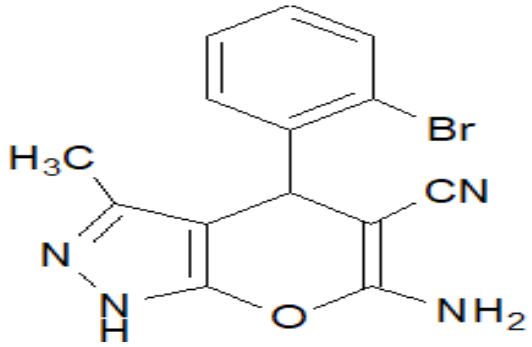
(19b)



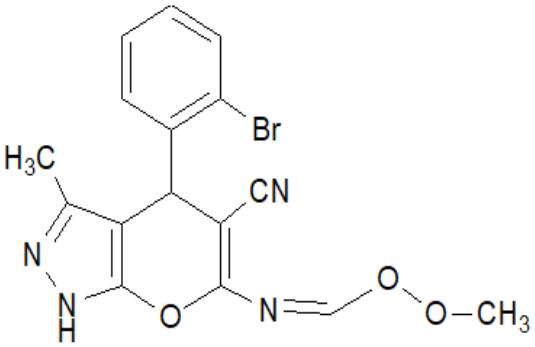
(19c)

Salae *et al.,* designed, developed and evaluated two fused pyrazole series derivatives pyrazolo-pyrimidine and dihydro-pyrano-pyrazole derivatives as promising scaffolds to make potent VEGFR-2 and EGFR inhibitors. Their anticancer activity was assessed *in vitro* next to the HEPG2 human cancer cells, using erlotinib and sorafenib as benchmarks.

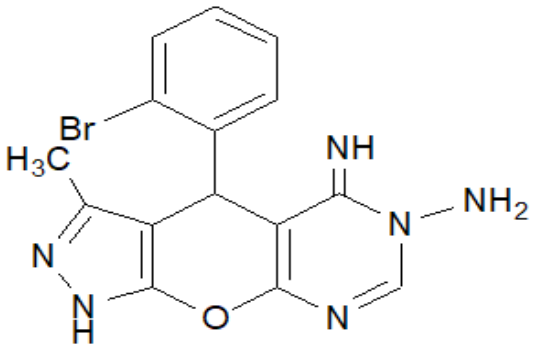
Out of these, seven entities, namely 20, 20a, 20b, 20c, 20d, 20f, 20g, and 20h, demonstrated anticancer activity nearly 10 times superior to erlotinib (with an IC_{50} of 10.6μM), exhibiting IC_{50} values between 0.31 and 0.71μM. Further, produced by synthesizing entities were experienced for their capability to slow down VEGFR-2 and EGFR. The outcomes pinpointed compound 20b as a top-tier EGFR inhibitor (IC_{50} of 0.06μM) and compound 20e as the majority effective vascular endothelial growth factor receptor-2 blocker (IC_{50} of 0.22μM). Interestingly, both compounds 20e and 20g exhibited strong inhibition of both EGFR and VEGFR-2, with 20g emerging as the standout in terms of both anticancer prowess against HepG2 cells and enzymatic inhibitory capacities. Docking experiments further substantiated these findings, showcasing how compounds 20e and 20g engage with vital amino acids in both enzymes to drive their efficacy. Initial analyses suggest that structures like dihydro-pyrano-pyrazole and pyrazolo-pyrimidine are intriguing starting points to craft potent inhibitors for EGFR and VEGFR-2[31].



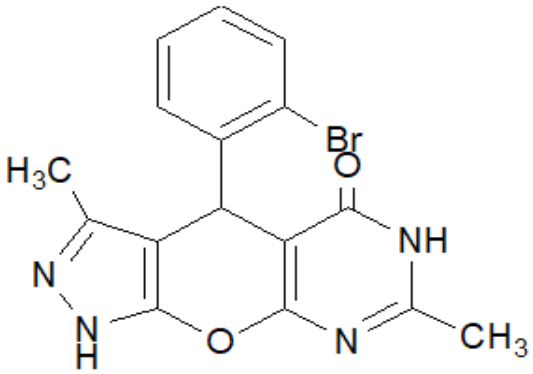
(20)



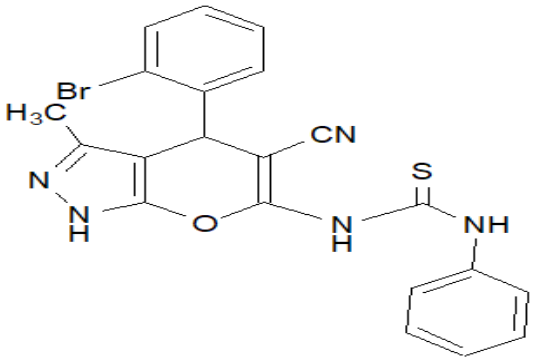
(20a)



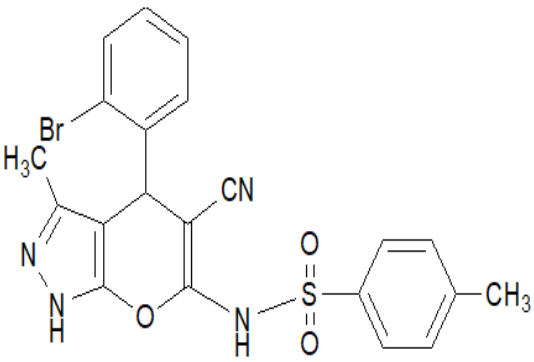
(20b)



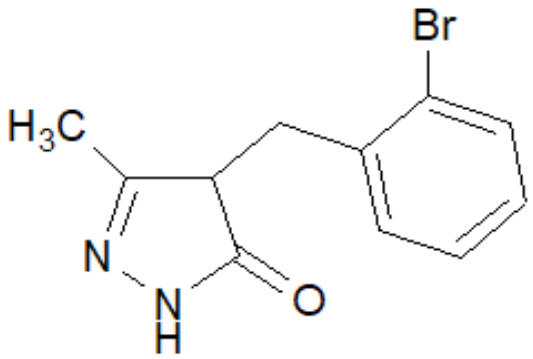
(20c)



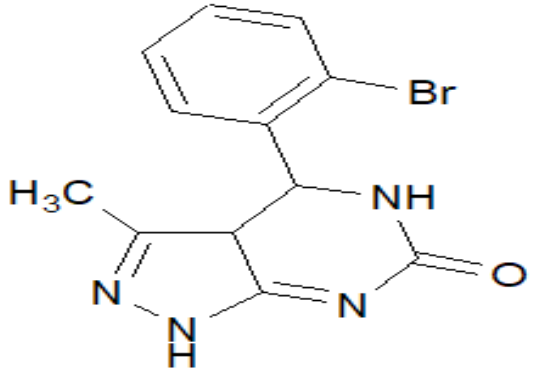
(20d)



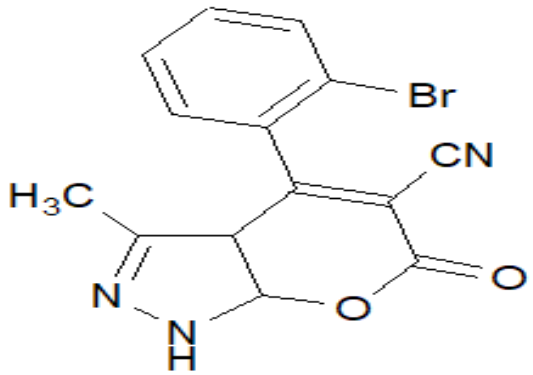
(20e)



(20f)

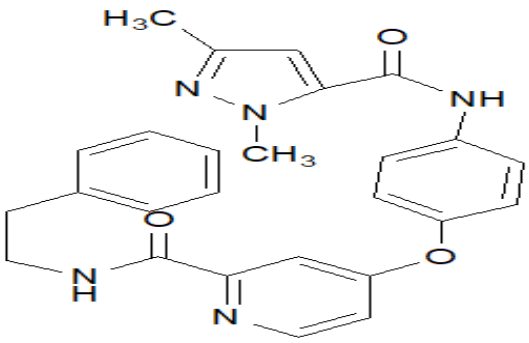


(20g)



(20h)

Novel pyrazole compounds were developed, synthesized, and their anti-proliferative properties as VEGFR-2 inhibitors assessed by Parameshwar Ravula *et al.,* A total of ten variants were created. Using the MTT assay, these molecules' in vitro anti-proliferative and vascular endothelial growth factor receptor-2 kinase inhibitory properties were assessed against two cancer cell lines. Notably, Compound 21 containing a phenylethyl ring demonstrated significant anti proliferative effects on and MCF-7and HT-29 cell lines with IC_{50} values of and 6.59 and 2.36 µM, correspondingly. Additionally, it showcased a compelling inhibitory movement beside vascular endothelial growth factor receptor-2 with an IC_{50} assessment of 1.89 µM. Docking studies further indicated that pyrazole derivatives are capable required to the vascular endothelial growth factor receptor-2 active site. They suggested that these compounds hold promise as primary candidates for creating anticancer treatments that focus on VEGFR-2 inhibition[32].



(21)

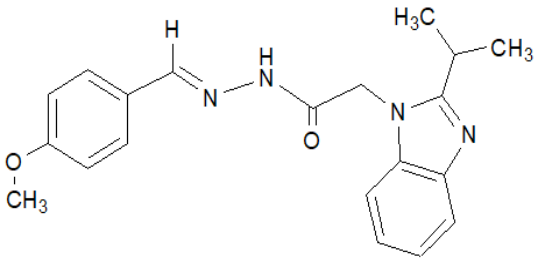
Benzimidazole derivatives

Benzimidazole represents a category of organic compounds characterized by a structure where a 6-membered benzene ring is conjoined with a 5-membered imidazole ring at its 4 and 5 positions. Since 1944, the benzimidazole nucleus has been acknowledged for its therapeutic significance. This heterocyclic system is found in an array of bioactive compounds, including antiviral, anticancer, and antibacterial agents. By optimizing substituents within this pharmacophore class, numerous effective drugs have been developed[33].

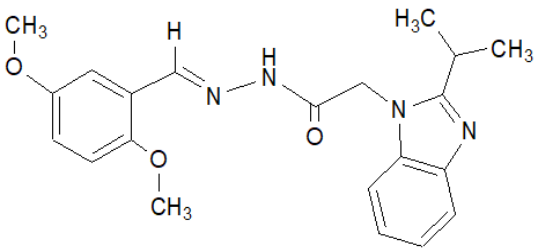
Heba T. Abdel-Mohsen *et al.,* rationally designed a novel sequence of 1,2-disubstituted benzo[d]imidazoles as VEGFR2 blockers aiming hepatocellular carcinoma. The primary objectives to be examine the consequence of substituting the 5-methylfuryl component at the 2-points of the recognized antiangiogenic 2-furylbenzimidazoles with an isopropyl component. This was done to gauge its impact on the cytotoxic activity against the HepG2 cell line and its inhibitory effect on VEGFR2. Derivatives as a result of the modification, formed showed advanced cytotoxic activity in association to the 2-furyl benzimidazole ,but they showed reasonable to a little inferior strength beside VEGFR2.(22,22a,22b) in comparison to sorafenib. As the study advanced, there was an additional refinement of the type IIIlike VEGFR2 benzimidazole structures. This was achieved by extending the side chain at their one-position to craft type II like VEGFR2 inhibitors. The prologue of varied benzyloxy groups seemed to significantly manipulate the activity levels. Impressively, the benzimidazoles 22c and 22d exhibited superior cytotoxicity relative to both sorafenib and other compounds in the series. When tested at 10μM, both these benzimidazoles, bearing the 3-benzyloxy phenyl group extension, manifested a wide-ranging antiproliferative activity against an array of NCI cancer cell lines.

Moreover, both 22c and 22d depicted encouraging VEGFR2 inhibitory performance in the HepG2 cell line, drawing an assessment to sorafenib. Remarkably, 22c was also discovered to have a strong tripleangiokinase inhibitory impact on VEGFR2, FGFR1, and PDGFR. Upon analyzing the HepG2 cell cycle post-treatment with 22c, it was discerned that there was a stop in the cell cycle at the G2/M phase, accompanied by the induction of a dose-reliant apoptotic effect.

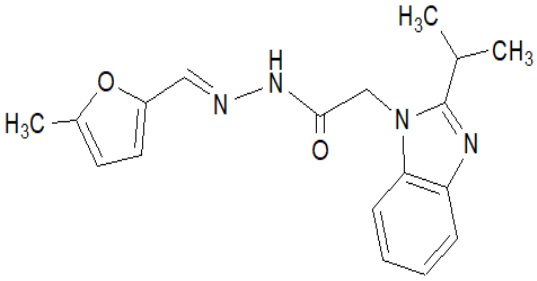
Compound docking simulations were also executed, which offered imminent into the securing efficacy of the benzimidazoles to the VEGFR2 required site. The findings indicated their potential to effectively engage and stabilize within the active site, establishing essential interactions with pivotal amino acids. From the observations and data acquired, one might infer that the series predominantly compounds 22c and 22d, stand as hopeful candidates. They can be further refined in anticipation of unearthing potent antiangiogenic agents for potential cancer treatments[34].



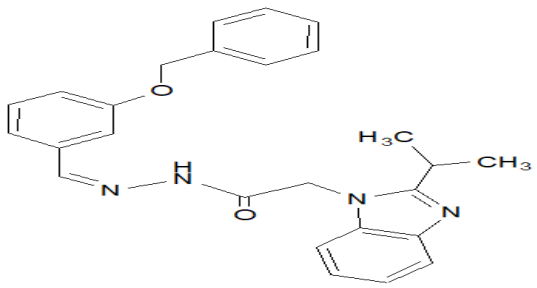
(22)



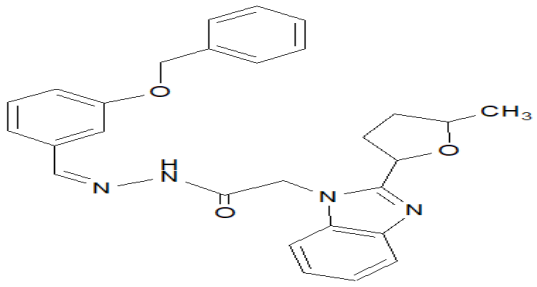
(22a)



(22b)

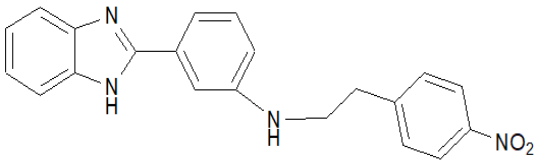


(22c)

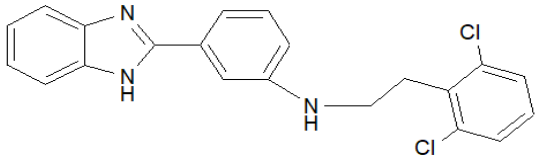


(22d)

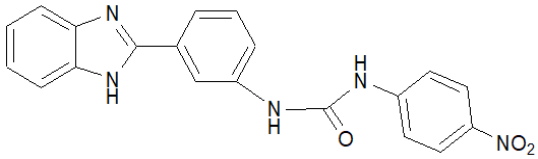
Amany S. Mostafa *et al.,* Three series of compounds based on 2-phenyl benzimidazole were developed and produced using easily accessible synthetic routes, and there in vitro cytotoxic activity against breast cancer (MCF-7) cell lines was assessed. Among the synthetic substances with an IC_{50} value of 3.37 µM, compound 23a was even more successful than the common medication doxorubicin. IC_{50} values for compounds 23b and 23d were 5.84 and 6.30 µM, respectively, indicating good cytotoxic action. Vascular endothelial growth factor receptor-2 enzyme assay exposed that ligands 23a, 23b, 23c, and 23d showed IC_{50} principles similar to that of the orientation medicine sorafenib, ranging from 6.7-8.9 nM[35].



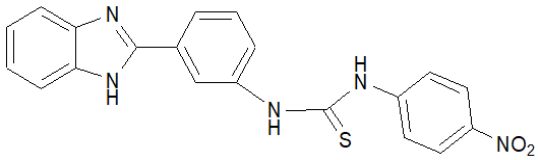
(23a)



(23b)

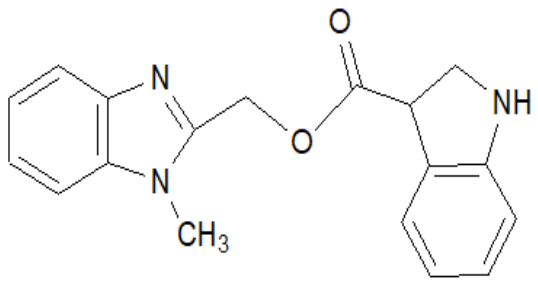


(23c)

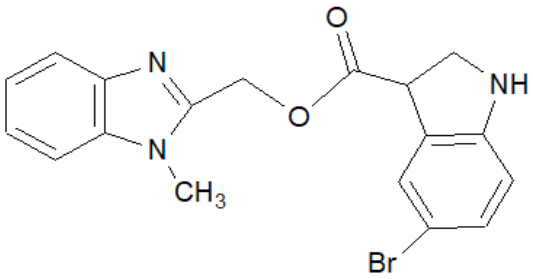


(23d)

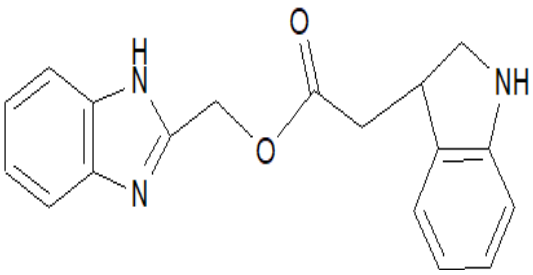
Yangyang Ding *et al.,* synthesized new derivatives of indole–benzothiazole and indole–benzimidazole, connected by various linkers, have been considered, synthesized, and posited as potential blockers for the VEGFR-2 tyrosine kinase. These synthesized compounds underwent cytotoxicity tests beside 4 human cancer cell lines (A549, HeLa, HT29, and MDA-MB-435) as well as the HUVEC. Concurrently, their latent to reduce the VEGFR-2 was assessed in vitro. Molecular docking was used to evaluate their binding connections with two conformations of the VEGFR-2 tyrosine kinase. Of the lot, molecules 24, 24a, 24b and 24c demonstrated significant blockers action beside the vascular endothelial growth factor receptor-2 kinase and displayed notable cytotoxicity, notably with IC_{50} values among 0.1 and 1µM, indicating their potential as broad-spectrum antitumor agents. This analysis paves the way for potential structural adaptations to create efficient VEGFR-2 inhibitors for the tyrosine kinase[36].



(24)

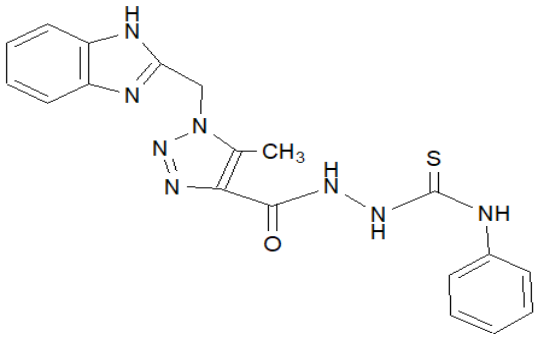


(24b)

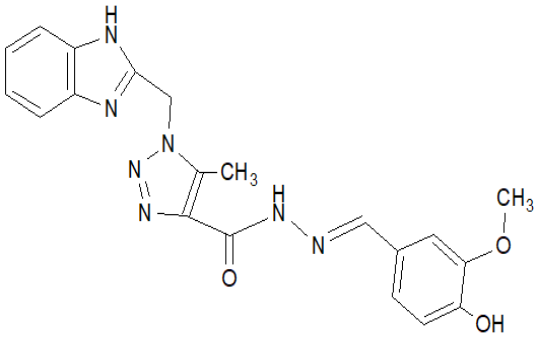


(24c)

Dina I. A. Othman *et al.,* has conducted a study on benzimidazole-triazolenhybrids as anticancer agents. The study was primarily focused on crafting multi-target-based benzimidazole-triazole hybrids, with an aspiration of advancing the quest for anticancer drug candidates that are target-specific. Two sequence of compounds synthesized were synthesized and were evaluated for their potential as multi-targeted cytotoxic agents. Their efficacy was assessed through various measures: inhibition of EGFR, VEGFR-2, Topo II and *in vitro* antitumor activity, DNA obligatory assays, cell cycle analysis, and the introduction of apoptosis. Notably, compounds 25, with IC_{50} values ranging from 3.87-8.34 IM, and 25a, ranging from 3.34-10.92 IM, emerged as the majority powerful contenders against cancer cell lines like MCF-7, HCT-116, HepG-2, and HeLa and were more assessed and displayed notable inhibitory actions against vascular endothelial growth factor receptor-2, EGFR, and Topo II inhibition. Particularly, the benzimidazole derivative compound 25 outperformed with impressive inhibitory action against EGFR, closely matching the efficacy of Gefitinib. Furthermore, it surpassed Doxorubicin in inhibiting Topo II. Molecular modeling studies further shed light on the antitumor potential and the inhibitory capacities of these compounds against EGFR, VEGFR-2, and Topo II. These studies highlighted their adeptness at binding proficiently with the principal active sites[37].



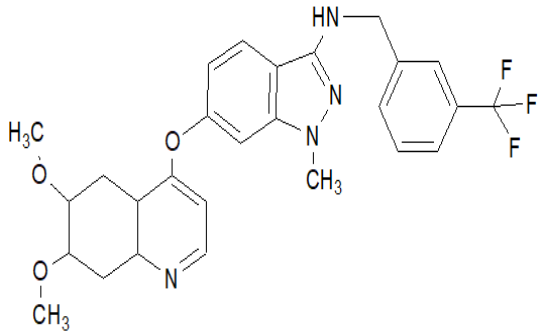
(25)



(25a)

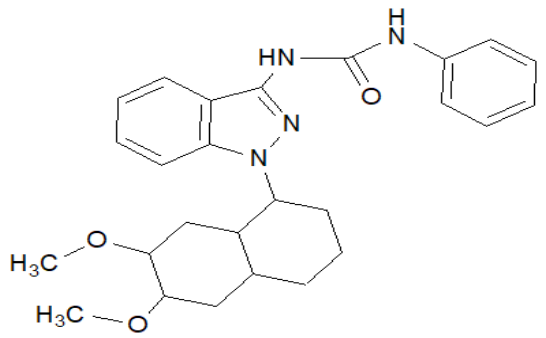
Indazoles derivatives

One of the most significant groups of heterocyclic compounds containing nitrogen are indazoles, which have a bicyclic ring formation collected of a benzene ring and pyrazole ring. David Bauer *et al.,* Identified a new family of strong and specific KDR inhibitors that included an indazole moiety. The major mediator of VEGF-induced migration, endothelial survival, tubular morphogenesis, proliferation, and sprouting is the Kinase inserts Domain having Receptor (KDR). In their study they modified Aryl-amino naphthyl compounds by replacing the 1-aminomethyl core since N-hydroxy-1-aminonaphthalene, a recognized metabolite of the 1-aminonaphthalene, has been characterized as carcinogenic and mutagenic. As indazole group is incorporated it showed excellent in selectivity, vitro potency, and pharmacokinetic properties. From the series compound 26 demonstrated high selectivity for KDR inhibition (IC_{50} = 0.001 IM), Compound 26's effectiveness in the VEGF-induced vascular permeability assay was encouraging.

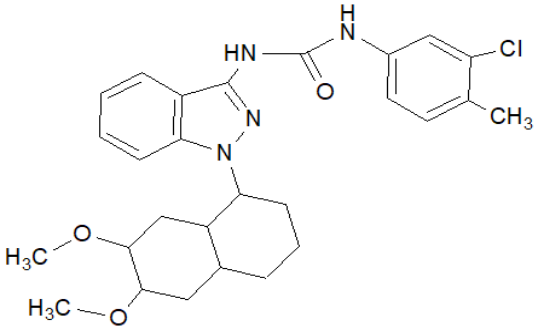


(26)

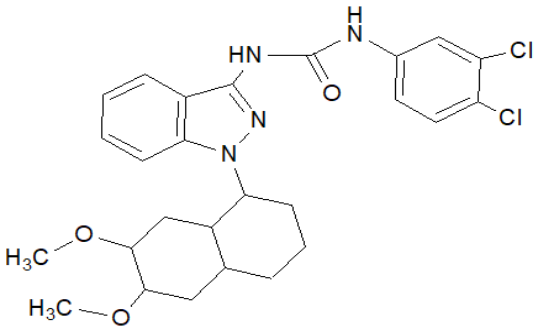
2 sequences of indazole-based derivatives were intended and created by Nevine M.Y. Elsayed *et al.,* The compounds' *in vitro* inhibitory accomplishment beside the VEGFR-2 kinase enzyme was assessed, and it was found that the second series was more potent than the first. Among these compounds, 27a, 27b, and 27c demonstrated the majority effective inhibitory exploit, with IC_{50} values of 5.4 nM, 5.6 nM, and 7 nM, respectively. In terms of cellular vascular endothelial growth factor receptor-2 blocker, molecules 27a as well as 27 b exhibited remarkable effects, with 80% and 99.6% inhibition of HUVEC propagation observed at an attention of 10 μM, respectively. Finally, the synthesized molecules were assessed for their in vitro anti-proliferative effects against the full NCI panel of cancer cell lines. Notably, ligand 27 along with 27b showed signifies growth inhibition percentages (GI %) of 93% and 130%, correspondingly. Furthermore, they exhibited superior performance compared to the FDA-approved drug sorafenib, both in terms of activity (GI_{50}) and protection (LC_{50}) beside numerous cell lines. Consequently, ligand 27b emerges as a talented applicant for tumor healing, operating during both antiangiogenic-independent and antiangiogenic-dependent mechanisms of action[38].



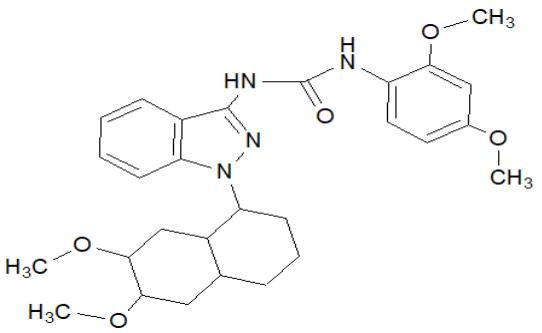
(27)



(27a)



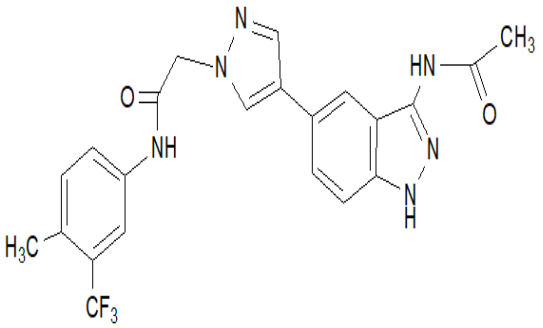
(27b)



(27c)

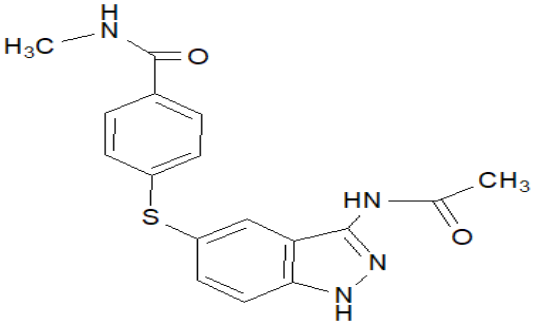
Xing-Rong Wang *et al.,* intended and amalgamated a fresh set of derivatives, 2-(4-(1H-indazol-6-yl)-1H-pyrazol-1-yl) acetamide, in addition to examine as VEGFR2 inhibitors by using a scaffold corresponding substitute approach. These derivatives were evaluated for their probable in enzymatic assays, anti-angiogenesis and anti-proliferation activities. The notable ligand 28, demonstrated moderate cytotoxic effects on human umbilical vein endothelial cells and exhibited selectivity over 500 times towards tumor HGC-27 cells compared to regular GES1 cells, highlighting its minimal toxicity. The SAR and molecular docking studies highlighted that the 6-(1H-pyrazol-4-

yl)-1H-indazol scaffold was critical for ensuring optimal movement. Study showed that W13 significantly hindered the trans well migration, colony formation, and invasion capabilities of HGC-27 cells in a dose-responsive method. Compound 28 showed anti-angiogenic effects with its ability to suppress pipe configuration and the appearance of p-vascular endothelial growth factor receptor-2 in human umbilical vein endothelial cells. The findings consistently indicate that Compound 28 holds potential as a talented guide applicant. Researchers advocate for continued study and structural optimization of Compound 28, anticipating that it could make easy the finding of potent VEGFR-2 inhibitors, thereby offering a new therapeutic avenue for gastric cancer treatment[39].



(28)

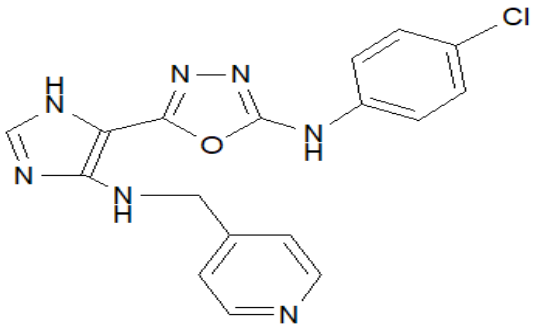
Zongru Jiang *et al.,* reported the identification and description of a novel VEGFR2 inhibitor compound number 28. it demonstrated high specificity when compared to kinases with similar structures like PDGFRs, FGFRs, CSF1R, and others. The compound showed a robust inhibitory impact on the VEGFR2 kinase in biochemical tests, with an IC_{50} value of 66 nmol/L. Similarly, its effectiveness against VEGFR2 autophosphorylation in cellular environments was marked by EC50 values of approximately 100 nmol/L. It also significantly curtailed the proliferation of VEGFR2-altered BaF3 cells with a GI_{50} value of 150 nmol/L. Beyond these findings; compound 29 showcased commendable anti-angiogenic performances in laboratory settings. Furthermore, it's *in vivo* pharmacokinetics were favorable, boasting a bioavailability exceeding 49%. The compound also proved its anti-angiogenic potency in zebra fish and mouse experiments, all without noticeable adverse effects[40].



(29)

Imidazole derivatives

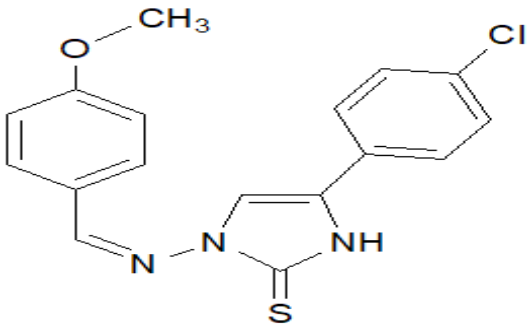
Alexander S. Kiselyov *et al.*, have been developed Novel imidazole derivatives as potent blockers of the vascular endothelial growth factor receptor-2. The compounds showed IC_{50} values below 100 nM in in vitro and cell-based assays. 4-Pyridylmethyl derivative compound number 30 provided the most effective activity with the IC_{50} value of 0.25 IM against vascular endothelial growth factor receptor-2[41].



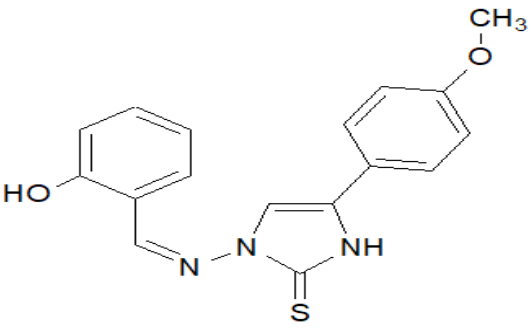
(30)

Ali H. Abu Almaaty *et al.,* synthesized, characterized a narrative sequence of imidazoles containing arylidene amino substituent at the N-1 place. These imidazole derivatives were then reviewed for their potential anticancer properties, particularly against three cancer cell lines: MCF-7 breast cancer, HepG2 liver cancer, and HCT-116 colon cancer cell lines. Among the compounds tested, Compound 31a displayed the maximum strength beside all three cell lines. When assessed for their blockers movement beside vascular endothelial growth factor receptor-2 and B-Raf kinase, compounds 31 and 31a demonstrated significant inhibitory effects compared to the reference drug erlotinib. As per their conclusion the compound number 31 as well as 31a show

promising potential as guide chemical entities for more structural optimization in the development of novel anticancer agents[42].



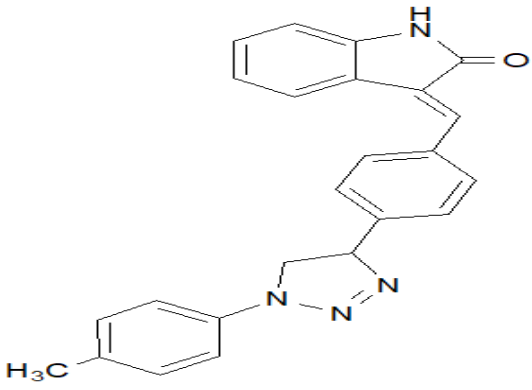
(31)



(31a)

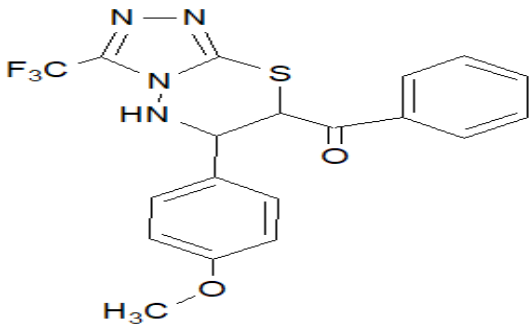
Triazole derivates

Wang, D *et al.,* created a series of a novel 7 indole-2-one derivatives supported on 1,2,3-triazole scaffolds in addition to they were assessed for their inhibitory activity on VEGFR-2. Between the produced molecule 32 shown superior inhibitory actions on MKN-45 cells and HT-29, less toxicity to HUVECs, and improved activity inhibition on VEGFR-2 than sunitinib. Western blot investigation exposed that compound 31 effectively reduced the phosphorylation of VEGFR-2 in HUVECs. Additionally, the inhibitory impact of compound 32 on angiogenesis was further validated in vivo through the utilization of VEGFR-2 specific fluorescent transgenic zebra fish. Wang d and team concluded that Compound 32 demonstrated promising potential as an inhibitor of VEGFR-2 phosphorylation, suggesting its potential utility in suppressing angiogenesis, a critical process in cancer. These findings highlighted its significance as a potential subject for additional research and development as an anti-angiogenic agent[43].

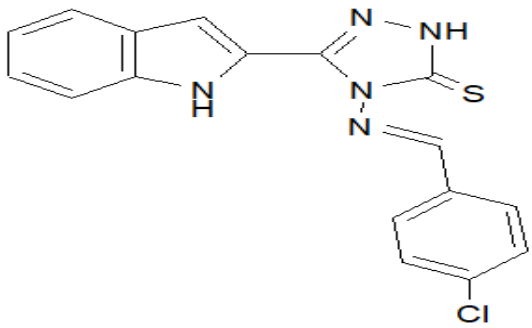


(32)

Amani M.R. Alsaedi and team developed an innovative succession of 3-mercapto-alternated 1, 2, 4-triazole derivatives and evaluated their potency as VEGFR2 inhibitors. In contrast to Sorafenib (IC_{50} = 0.088 µM), the majority of molecules exhibited talented inhibitory activity, The triazolo thiadiazole derivative 33 appeared as the majority vigorous one (IC_{50} = 0.057 µM) compound 33a showed activity similar to sorafenib against HepG2 and 4.1 times against Huh7[44].



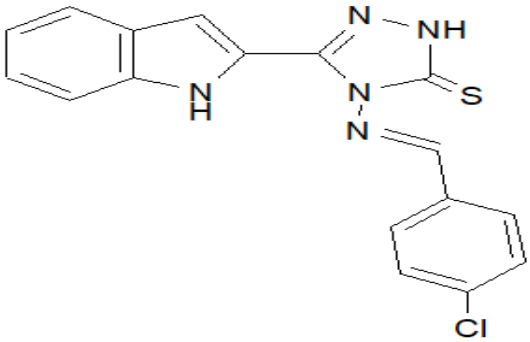
(33)



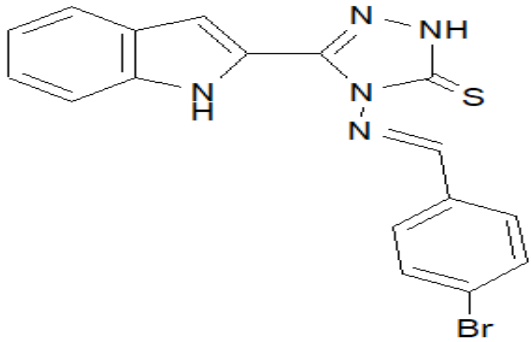
(33a)

Sami A. Al-Hussain and team discovered a novel series of indolyl 1,2,4-triazole hybrids as potent VEGFR-2 inhibitors with anti-renal cancer possible. Every objective molecule

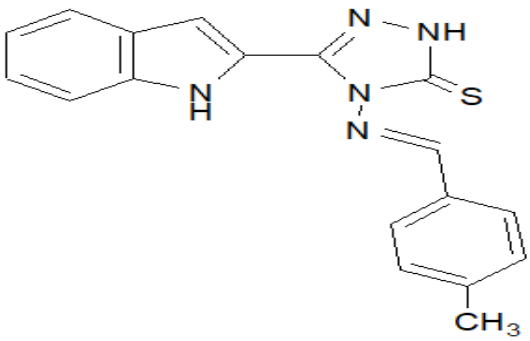
displayed impressive sub micromolar inhibition of the VEGFR-2 kinase enzyme. Notably, analogs 34b, 34c, and 34e appeared since the mainly powerful, surpassing the VEGFR-2 inhibitory movement of the reference drug sunitinib. Furthermore, ligand 34, 34d, 34f, and 34h exhibited excellent vascular endothelial growth factor receptor-2 blocker action, equivalent to that of sunitinib. This highly promising ligand were then evaluated *in vitro* for their anticancer activity adjacent to two human renal cancer cell lines, demonstrating substantial growth inhibition, with compounds 34a, 34c, 34g, and 34h standing out as 3-5 times extra strong than sunitinib aligned with the CAKI-1 cell line. Remarkably, ligand 34f displayed twice the strength of sunitinib aligned with the A498 cell line. Additionally, analogues 34d and 34hexhibited a protection outline superior to with the intention of sunitinib when tested beside normal human renal cells. Lastly, the docking analysis revealed that the compounds formed hydrogen-bonding and hydrophobic connections with solution remains within the vigorous position of the VEGFR-2 kinase enzyme, shedding light on their potential as encouraging prospects for more anticancer drug development[45].



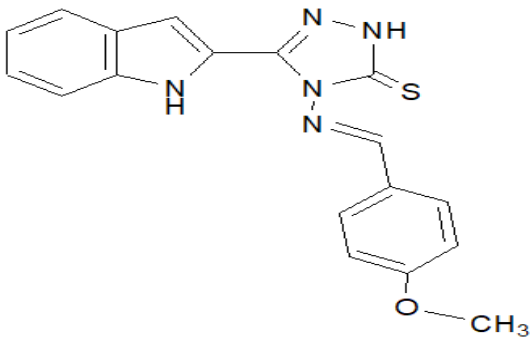
(34)



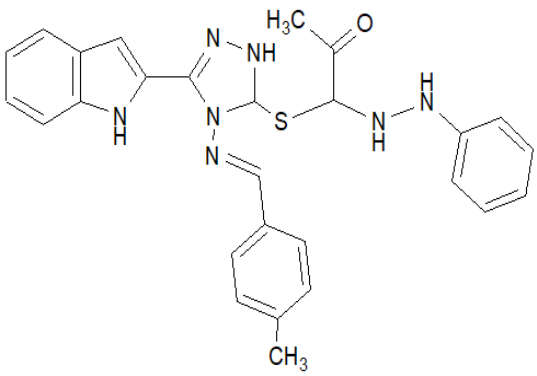
(34a)



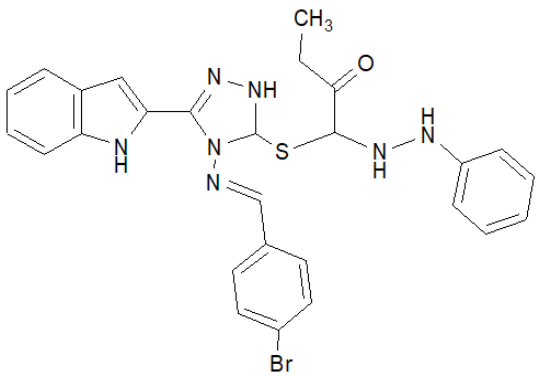
(34b)



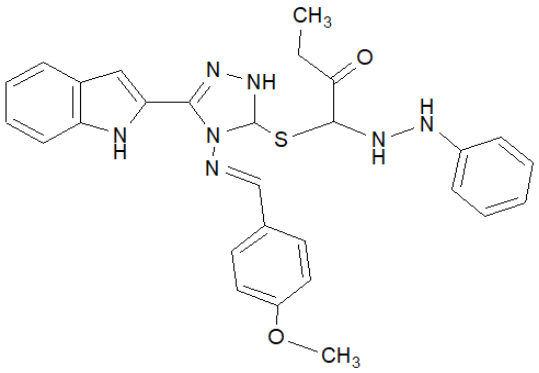
(34c)



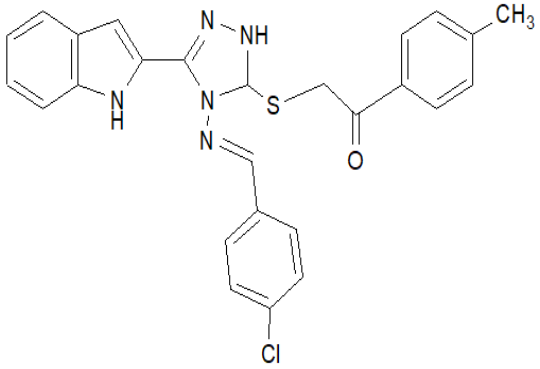
(34d)



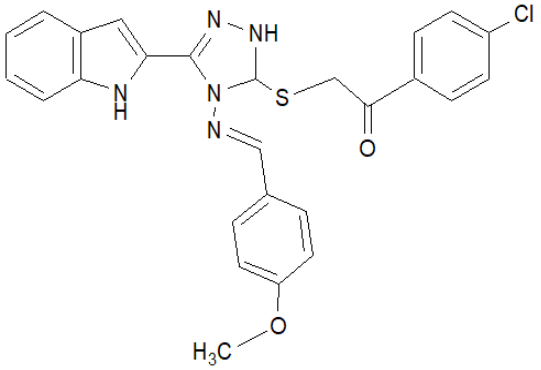
(34e)



(34f)



(34g)



(34h)

CONCLUSION

In conclusion, this comprehensive scientific review delves into the promising realm of synthetic vascular endothelial growth factor (VEGF) inhibitors, shedding light on their potential as innovative therapeutic agents across various medical disciplines. The synthesis and development of VEGF inhibitors represent a crucial advancement in the field of biomedicine, offering tailored and customizable solutions to target angiogenesis and vascular permeability. Through extensive preclinical and clinical studies, these synthetic inhibitors have demonstrated efficacy in treating various types of cancer. The versatility of synthetic VEGF inhibitors, combined with their ability to mitigate the limitations associated with natural counterparts has the potential to redefine treatment paradigms and improve patient outcomes. Nevertheless, the complexity of angiogenesis regulation and the need for continued investigation into the safety profile and resistance mechanisms underscore the significance of continuing study efforts within this meadow. In the foreseeable future, synthetic VEGF inhibitors are poised to play more and more central role in the arsenal of therapeutic options, offering hope to patients worldwide grappling with a spectrum of debilitating diseases.

ACKNOWLEDGMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The author declare that we have no conflict of interest.

REFERENCES

1. World Health Organization. Cancer [Internet]. www.who.int., **2022**.
2. What Is Cancer?-National Cancer Institute [Internet]. www.cancer.gov. **2007**.
3. Jiang, X.; Wang, J.; Deng, X.; Xiong, F.; Zhang, S.; Gong, Z. The role of microenvironment in tumor angiogenesis., *J. Exp. Clin. Cancer Res.*, **2020**, *30*, 39(1).

4. Shibuya, M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies., *Genes & Cancer.*, **2011**, *2*(12), 1097–105.
5. Hicklin, D.J.; Ellis, L.M.. Role of the Vascular Endothelial Growth Factor Pathway in Tumor Growth and Angiogenesis., *J. Clin. Oncol.*, **2005**, *23*(5), 1011–27.
6. Ferrara, N.; Gerber, H.P.; LeCouter, J. The biology of VEGF and its receptors., *Nature Medicine.*, **2003**, *9*(6), 669–76.
7. VEGF signaling pathway [Internet] available from https://www.cusabio.com/pathway/VEGF-signaling-pathway.
8. Pandey, A.K.; Singhi, E.K.; Arroyo, J.P.; Ikizler, T.A.; Gould, E.R.; Brown, J. Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor–Associated Hypertension and Vascular Disease., *Hypertension.*, **2018**, *71*(2).
9. Al-Sanea, M.M.; Chilingaryan, G.; Narek, A,; Sargsyan, A.A.; Hovhannisyan, S.; Gasparyan, H. Identification of Novel Potential VEGFR-2 Inhibitors Using a Combination of Computational Methods for Drug Discovery., *Life.*, **2021**, *11*(10), 1070–0.
10. Khaled, El.A.dl.; Sakr, H.; Yousef, R.G.; Ahmed, Metwaly, A.M.; Elhendawy, M.A. Discovery of new quinoxaline-2(1H)-one-based anticancer agents targeting VEGFR-2 as inhibitors: Design, synthesis, and anti-proliferative evaluation., *BIOORG CHEM.*, **2021**, *114*, 105105–5.
11. Eissa, I, H.; ElHelby, A.A.; Mahdy, H.A.; Khalifa, M.M.; El-Nagar, H.A.; Ahmed. Discovery of new quinazolin-4(3H)-ones as VEGFR-2 inhibitors: Design, synthesis, and anti-proliferative evaluation., *Bioorg Chem.*, **2020**, *105*, 104380–0.
12. Letícia, M.; Lídia, M.L.; Tesch, R.; Mauricio, C.; Totzke, F.; Michael, H.G.; Kubbutat. Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors., *Eur. J. Med. Chem.*, **2014**, *71*, 1–14.
13. Fan, Haoru.; Wei, D.; Zheng, K.; Qin, X.M.; Yang, L.; Yang, Y. Discovery of Dioxino[2,3-f] quinazoline derivative VEGFR-2 inhibitors exerting significant antipro-liferative activity in HUVECs and mice., *Eur. J. Med. Chem.*, **2019**, *175*, 349–56.
14. Wei, D., Fan, H.; Zheng, K.; Qin, X.; Yang, L.; Yang, Y.; Synthesis and anti-tumor activity of [1,4] dioxino [2,3-f] quinazoline derivatives as dual inhibitors of c-Met and VEGFR-2., *Bioorganic Chemistry.*, **2019**, *88*, 102916.
15. Pathak, P.; Shukla, P.K.; Kumar, V.; Kumar, A.; Verma, A. Quinazoline clubbed 1,3,5-triazine derivatives as VEGFR2 kinase inhibitors: design, synthesis, docking, in vitro cytotoxicity and in ovo antiangiogenic activity., *Inflammopharmacology.*, **2018**, *26*(6), 1441–53.
16. Surjana, D.; Halliday, G.M.; Damian, D.L. Role of Nicotinamide in DNA Damage, Mutagenesis, and DNA Repair., *J. Nucleic Acids.*, **2010**, 2010, 1–13.
17. Elkaeed, E.B.; Youse, R.G.; Khalifa, M.M.; Ibrahim, A.; Ahmed, I. Discovery of New VEGFR-2 Inhibitors: Design, Synthesis, Anti-Proliferative Evaluation, Docking, and MD Simulation Studies., *Molecules.*, **2022**, *27*(19), 6203–3.
18. Choi, H.E.; Yoo, M.S.; Choi, J.H.; Lee, J.Y.; Kim, J.H.; Kim, J.H. BRN-103, a novel nicotinamide derivative, inhibits VEGF-induced angiogenesis and proliferation in human umbilical vein endothelial cells., *BMCL.*, **2011**, *21*(21), 6236–41.
19. Choi, H.; Choi, J.; Jae, Y. L.; Je, H. K.; Ji, H. K.; Joon, K. L. Synthesis and evaluation of nicotinamide derivative as anti-angiogenic agents., *BMCL.*, **2013**, *23*(7), 2083–8.
20. Peng, M.; Shi, L.; Ke, S. Nicotinamide-based diamides derivatives as potential cytotoxic agents: synthesis and biological evaluation., *Chem. Cent. J.*, **2017**, 24, 11(1).
21. Yousef, R.G.; Alaa, E.; Ibraheem, A.; Eldehna, W.M.; ElMetwally, S.A. Anti-cancer and immunomodulatory evaluation of new nicotinamide derivatives as potential VEGFR-2 inhibitors and apoptosis inducers: *in vitro* and *in silico* studies., *J Enzyme Inhib Med Chem.*, **2022**, *37*(1), 2206–22.
22. Kilic-Kurt, Z. Synthesis of Novel Oxadiazole Derivatives, Molecular Properties Prediction, and Molecular Docking Studies., *JOTCSA.*, **2020**, *7*(3), 753-74.

23. Bilal, M.; Syeda, A.E.; Zargar, S.; Akhtar, N.; Wani, T.A.; Riaz, N. Computational Investigation of 1, 3, 4 Oxadiazole Derivatives as Lead Inhibitors of VEGFR 2 in Comparison with EGFR: Density Functional Theory, Molecular Docking and Molecular Dynamics Simulation Studies., *Biomolecules*., **2022**, *12*(11), 1612–2.
24. Hagras, M.; Saleh, M.A.; Ezz, E.R.; Abuelkhir, A.A.; Khidr, E.G.; El-Husseiny, A.A. 1,3,4-Oxadiazole-naphthalene hybrids as potential VEGFR-2 inhibitors: design, synthesis, antiproliferative activity, apoptotic effect, and *in silico* studies., *J Enzyme Inhib Med Chem*., **2021**, *37*(1), 386–402.
25. Qiao, F.; Yin, Y.; Shen, Y.N.; Wang, S.F.; Sha, S.; Wu, X. Synthesis, molecular modeling, and biological evaluation of quinazoline derivatives containing the 1,3,4-oxadiazole scaffold as novel inhibitors of VEGFR2., *RSC Advances*., **2015**, *5*(26), 19914–23.
26. Aziz, M.A.; Serya, R.A.T.; Lasheen, D.S.; Abdel-Aziz, A.K.; Esmat, A.; Mansour, A.M. Discovery of Potent VEGFR-2 Inhibitors based on Furopyrimidine and Thienopyrimidne Scaffolds as Cancer Targeting Agents., *Sci. Rep*., **2016**, *15*, 6(1).
27. Oguro, Y.; Miyamoto, N.; Okada. K.; Takagi, T.; Iwata, H.; Awazu, Y. Design, synthesis, and evaluation of 5-methyl-4-phenoxy-5H-pyrrolo[3,2-d]pyrimidine derivatives: Novel VEGFR2 kinase inhibitors binding to inactive kinase conformation., *BMCM*., **2010**, *18*(20), 7260–73.
28. Sun, W.; Hu, S.; Fang, S.; Yan, H. Design, synthesis and biological evaluation of pyrimidine-based derivatives as VEGFR-2 tyrosine kinase inhibitors., *BIOORG CHEM*. **2018**, *78*, 393–405.
29. El-Metwally, S.A.; Abou-El-Rega,I M.M.; Eissa, I.H.; Mehany, A.B.M.; Mahdy, H.A.; Elkady, H. Discovery of thieno[2,3-d]pyrimidine-based derivatives as potent VEGFR-2 kinase inhibitors and anti-cancer agents., *BIOORG CHEM*., **2021**, *112*, 104947.
30. Alkamaly, O.M.; Altwaijry, N.; Sabour, R.; Harras, M.F. Dual EGFR/VEGFR2 inhibitors and apoptosis inducers: Synthesis and antitumor activity of novel pyrazoline derivatives., *Arch. Pharm*., **2020**, *354*(4), 2000351.
31. Saleh, N.M.; El-Gazzar, M.G.; Aly, H.M.; Othman, R.A. Novel Anticancer Fused Pyrazole Derivatives as EGFR and VEGFR-2 Dual TK Inhibitors., *Front. Chem*., **2020**, *24*, 7.
32. Ravula, P.; Vamaraju, H.B.; Paturi, M.; Sharath Chandra, J.N.G.N. Design, synthesis, in silico and antiproliferative evaluation of novel pyrazole derivatives as VEGFR-2 inhibitors., *Arch. Pharm*., **2017**, *351*(1), 1700234.
33. Hernández-López, H.; Tejada-Rodríguez, C.J.; Leyva-Ramos, S. A Panoramic Review of Benzimidazole Derivatives and their Potential Biological Activity., *Mini Rev Med Chem*., **2022**, *22*(9), 1268–80.
34. Abdel-Mohsen, H.T.; Abdullaziz, M.A.; El Kerdawy, A.M.; Ragab, F.A.F.; Flanagan, K.J.; Mahmoud, A.E.E. Targeting Receptor Tyrosine Kinase VEGFR-2 in Hepatocellular Cancer: Rational Design, Synthesis and Biological Evaluation of 1,2-Disubstituted Benzimidazoles., *Molecules*., **2020**, *25*(4), 770.
35. Mostafa, A.A.; Gomaa, R.; Elmorsy, M.A. Design and synthesis of 2phenyl benzimidazole derivatives as VEGFR 2 inhibitors with antibreast cancer activity., *Chem Biol Drug Des*., **2018**, *93*(4), 454–63.
36. Ding, Y.; Li, K.; Zhao, X.; YingtaoLv, Yu. R.; Kang, C. Design, synthesis, and antitumor activity of novel benzoheterocycle derivatives as inhibitors of vascular endothelial growth factor receptor-2 tyrosine kinase., *J. Chem. Res*., **2020**, *44*(5-6), 286–94.
37. Dina, Hamdi, A.; Tawfik, S.S.; Elgazar, A.A.; Mostafa, A.S. Identification of new benzimidazole-triazole hybrids as anticancer agents: multi-target recognition, in vitro and in silico studies., *J Enzyme Inhib Med Chem*., **2023**, *18*, 38(1).
38. Elsayed, N.M.Y.; Serya, R.A.T.; Tolba, M.F.; Ahmed, M.; Barakat, K.; Jiang. Z.; Wang, L.; Liu, X.; Chen. C.; Wang, B.; Wang, W. Discovery of a hig.; Abou El Ella DA, et al. Design, synthesis, biological evaluation and dynamics simulation of indazole derivatives with antiangiogenic and antiproliferative anticancer activity., *BIOORG CHEM*., **2019**, *82*, 340–59.

39. Wang, X.R.; Wang, S.; Li, W.B.; Xu, K.Y.; Qiao, X.P.; Jing, X.L. Design, synthesis and biological evaluation of novel 2-(4-(1H-indazol-6-yl)-1H-pyrazol-1-yl) acetamide derivatives as potent VEGFR-2 inhibitors., *Eur. J. Med. Chem.*, **2021**, *213*, 113192.
40. hly selective VEGFR2 kinase inhibitor CHMFL-VEGFR2-002 as a novel anti-angiogenesis agent., *Acta Pharm.Sin.*B., **2020**, *10*(3), 488–97.
41. Kiselyov, A.S.; Semenova, M.N., Hetaryl imidazoles: A novel dual inhibitors of VEGF receptors I and II., *BMCL.*, **2006**, *16*(5), 1440–4.
42. Abu, A,H.; Toson, E.E.M.; ElSayed, E.H.; Tantawy, M.A.; Fayad, E.; Abu, O.A. 5-Aryl-1-Arylideneamino-1H-Imidazole-2(3H)-Thiones. Synthesis and In Vitro Anticancer Evaluation., *Molecules.*, **2021**, *26*(6), 1706–6.
43. De-pu, W.; Kai-li, L.; Xin-yang, L.; Guo-qing, L.; Wen-han, X.; Xin-hua, Q. Design, synthesis, and in vitro and in vivo anti-angiogenesis study of a novel vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitor based on 1,2,3-triazole scaffold., *Eur. J. Med. Chem.*, **2021**, *211*, 113083
44. Alsaedi, A.M.R.; Almehmadi, S.J.; Farghaly, T.A.; Harras, M.F.; Khalil, K.D. VEGFR2 and hepatocellular carcinoma inhibitory activities of trisubstituted triazole derivatives., *J. Mol. Struct.*, **2022**, *1250*, 131832.
45. AlHussain, S. A.; Farghaly, T. A.; Zaki, A.; Hanan, G. Abdulwahab.; AlQurashi, N.T.; Muhammad, Z. A. Discovery of novel indolyl-1,2,4-triazole hybrids as potent vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitors with potential anti-renal cancer activity., *Bioorg Chem.*, **2020**, *105*, 104330.