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REVIEW

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Exploring the potential of small molecules of dual c-Met and VEGFR inhibitors for advances and future drug discovery in cancer therapy

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Abstract

Background Cancer is uncontrolled cell proliferation that has the potential to invade other tissues and cells. The first three most prevalent cancers are breast, lung, and colon cancer. The widest family of kinase enzymes is receptor tyrosine kinases (RTKs) which are aimed by several chemotherapy medicines. The vascular endothelial growth factor (VEGFR), a well-known type IV tyrosine kinase receptor, is an effective biological target for the development of angiogenesis-related cancer treatments. The hepatocyte growth factor (also known as mesenchymal–epithelial transition factor) triggers the activation of the c-Met tyrosine kinase receptor, which controls several biological processes including cell division, survival, and proliferation.

Main body In this review, we summarized the various dual inhibitors of VEGFR and c-MET receptors which are active for therapeutic action against cancer. Combination of some VEGFR and c-Met inhibitors also shows synergistic action. The developed dual inhibitors of VEGFR and c-MET such as quinolones and quinazolines derivatives, pyridine and pyrimidine derivatives, oxindole moiety and triazine derivatives are most potent for the same. Dual inhibitors of VEGFR and c-MET hold significant promise in improving cancer therapy by enhancing treatment efficacy, reducing resistance, and potentially improving patient outcomes. Clinical trials are currently being conducted on a few of them and other compounds are being under investigation. Inhibiting VEGFR and c-Met pathway activity will be discussed as novel therapeutic strategies for advanced development in treating cancer. The research progress in this review is fetched up to the current year.

Conclusion Apart from the development of cancer treatment still cancer is listed as a deadly disease, due to its toxicity and resistance to treatment. Hence, the novel approach is necessary to overcome the cancer. The VEGFR and c-MET inhibitors as dual inhibitors may be more significant in future clinical anticancer treatments.

Keywords Cancer, VEGF receptor, C-MET receptor, Anticancer drug, Dual inhibition, Research progress

Background

Cancer, one of the most threatening diseases known to human beings, has been studied for centuries by not only medical doctors but also researchers from various technical fields. Cancer is uncontrolled cell growth potentially invade the other parts and cells [1]. Cancer cells interrupt normal cell growth, cellular activities, differentiation and programmed cell death. According to WHO,

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the worldwide death rate of cancer was nearly 9.7 million deaths in 2022 or approximately one in five deaths and 20 million new cases were identified [2, 3]. Mostly, the risk factors for cancer include excessive alcohol consumption, tobacco use, and lack of regular exercise, etc. [4, 5]. There are various forms of cancer such as breast cancer, rectal cancer, lymphoma, colon cancer, basal cell cancer, prostate cancer, leukemia, melanoma, and lung cancer. [6, 7]. Among them, the top three most prevalent cancers are breast, lung, and colon cancer [8]. Worldwide, approximately 2.3 million new cases of breast cancer (11.6%) and 2.5 million new cases of lung cancer (12.4%) are diagnosed every year [9]. 1.9 million new cases of colon cancer were observed [10, 11].

For the treatment of cancer, various methods have been available, including radiation therapy, photo-thermal therapy, chemotherapy, immunotherapy, etc. [12]. There are many pathway targets available the for treatment of cancer such as tyrosine kinase inhibitors. The most effective strategy is to target the tyrosine kinase receptor for potent antibody production in chemotherapy development. Another essential target is IL-6/JAK/STAT3 pathway which prevent cancer related to inflammation. Other targets for cancer like interruption of Wnt/β-catenin signaling and TGFβ signaling pathway, also target for various type of cancer. The suppression of Phosphoinositide 3-kinases (PI3Ks) enzyme and matrix metalloproteinases ((MMPs) is also responsible) for therapeutic approach of cancer [13–15].

Distinct chemotherapeutic drugs target different members of the broad family of kinase enzymes known as receptor tyrosine kinases (RTKs). RTKs, which have a high affinity for a variety of polypeptide cytokines, hormones, and growth factors, are cell surface receptors. There have been discovered so far non-receptor (NRTKs) and receptor (RTKs) tyrosine kinases which are approximately at least 32 and 58, respectively [16–18]. Tyrosine amino acids are phosphorylated by RTKs in a number of proteins with the help of ATP (a -phosphoryl group donor). The signal transduction pathway is activated by this phosphorylation, which is a critical step in the differentiation, proliferation, migration, and anti-apoptotic pathways [19–21].

The aim of a tyrosine kinase inhibitor (TKI) is to hinder the targeted kinase from executing its role in catalyzing phosphorylation. There are various tyrosine kinase inhibitors (TKIs) such as, ROS1, EGFR, TRK, VEGF, ALK, MET, NTRK, RET, MEK, PDGFR, HER2 and KIT [22–25]. These TKIs have significantly improved cancer treatment, and as a result, they are now important targets for new drugs [26, 27]. It is reported that a huge amount of these tumor angiogenesis cases are related to metastasis; hence, dual inhibitors which are able to interact with VEGFR and c-Met at the same time could be a promising approach for present and future cancer therapies. As a matter of fact, we know very little about the real structures and function of most anti-cancer targets because a wide range of different experimental techniques (binding assay, kinase assay, computational modeling, and so on) are required from the very beginning of a rational drug design. Moreover, a number of rare skills, such as protein crystallization for X-ray analysis and nuclear magnetic resonance (NMR), are also needed in order to understand the conformational which is critically important to the function of proteins. However, huge progress has been made in recent years both in technology and in knowledge (Fig. 1).

Main text

VEGFR (vascular endothelial growth factor receptor)

The kinase insert domain receptor often referred as VEGFR is a type IV receptor that is widely acknowledged as a powerful target for developing anticancer therapy concerning angiogenesis [28–30]. As a result, it significantly affects tumor vascular endothelial cells' migration and growth. Particularly important during angiogenesis are interaction of vascular endothelial growth factors with membrane receptors. Overexpression of VEGF and its receptors has been identified in many solid tumors, and the VEGF/VEGFR signaling pathway is crucial for tumor vascularization. The Flt-1, also known as VEGFR-1, KDR receptor (VEGFR-2), and Flt-4, also known as VEGFR-3, family of VEGFRs specifically interacts with VEGF-A, B, C, and D, which are VEGF isoforms, and PIGF, which stands for placental growth factor [31–36].

VEGFR-1, an RTK with kinase impairment, may signal in the presence of a receptor heterodimer [37, 38]. By using receptor homo- and heterodimerization, ligand-trapping, and other processes, VEGFR-1 controls angiogenesis [39]. Another crucial receptor that is essential for angiogenesis and vasculogenesis is VEGFR-2 [40, 41]. This receptor consists of three components such as the TK domain-containing hydrophobic transmembrane region, carboxyl-terminal and region with an extracellular Ig-like domain [42].In vitro, VEGFR-2 stimulates numerous signaling pathways and a wide range of biological reactions [43]. The principal regulator of angiogenesis is VEGF-A, often known as VEGF. Endothelial cell migration and proliferation are stimulated by VEGF binding to VEGFR-2, which also controls vascular permeability as shown in Fig. 2. In recent years, multi-targeted TKIs with a VEGFR association have been developed into potent anti-tumor agents for solid malignancies [44, 45].

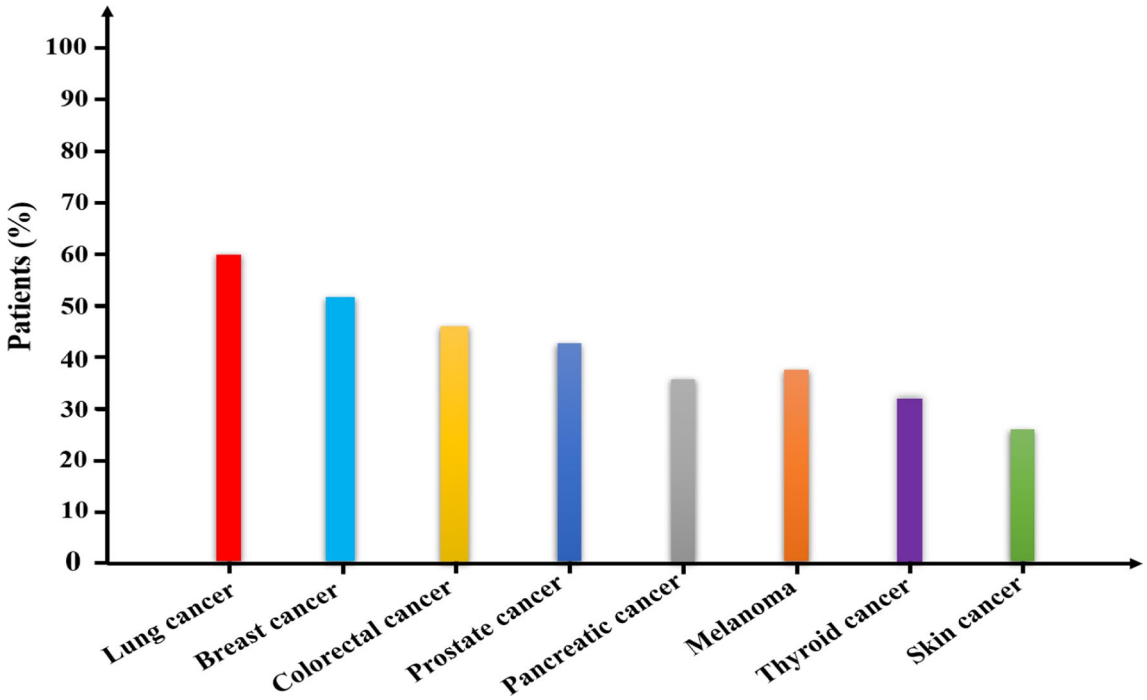


Fig. 1 Graphical representation of reported angiogenesis cases related to cancer types

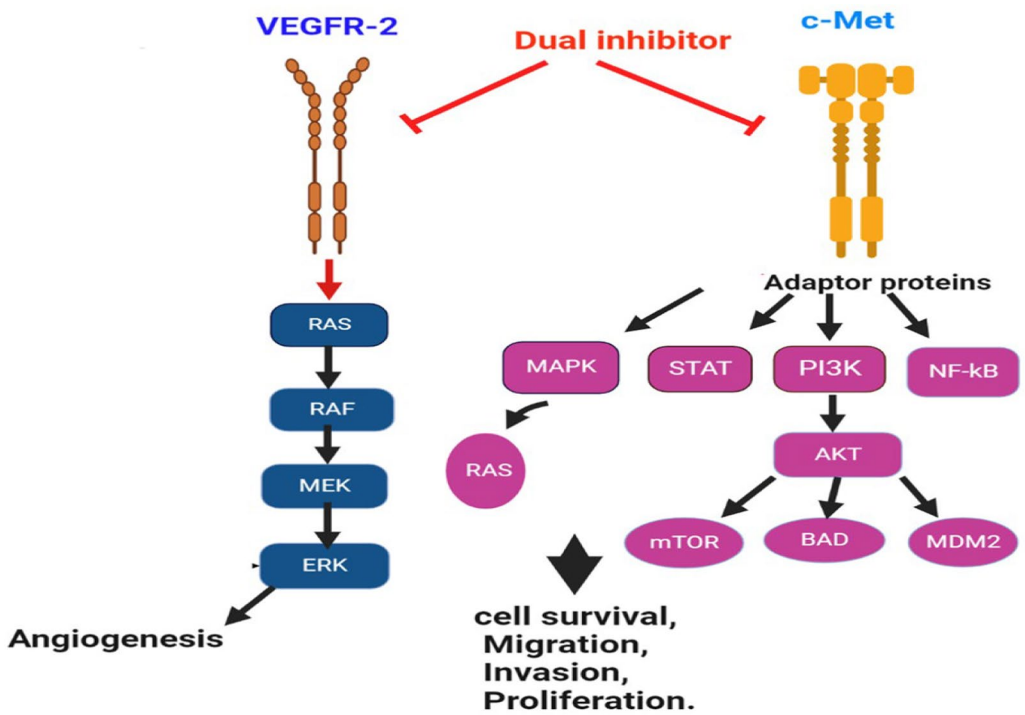


Fig. 2 The cross-talk between VEGFR and c-MET to express molecular pathway

c-MET receptor

In various types of solid tumors, among the most popular c-MET is genetically amplified and deregulated RTKs, making it a popular therapeutic target. The receptor known as MET (mesenchymal–epithelial transition factor), frequently denoted as c-MET or the receptor for hepatocyte growth factor, is the subsequent phrase and joins the mesenchymal and epithelial layers of cells (HGFR) [46, 47]. The c-MET receptor is compensated by a 50-kDa α-chain spanning the membrane and a 145-kDa β-chain located externally, which forms a heterodimer190-kDa glycoprotein. A disulfide bond connects the TM β- chain and α-extracellular chain [48]. Numerous signaling cascades, including STAT3, PI3K/AKT, RAS and SRC/FAK, are activated by the HGF/c-Met pathway and help to promote angiogenesis either directly by promoting the growth of endothelium cells, or by increasing the manifestation of angiogenic mediators as shown in Fig. 2 [49]. Cell division, migration, mobility, and penetration are affected by the interaction between MET and its corresponding molecule, HGF, which additionally triggers several signaling routes. Deregulation and activation of c-MET can cause uncontrolled cell proliferation and differentiation, which aids in the development of cancer [50, 51]. In 30–70% of CRC tumors, c-Met overexpression has been seen [52, 53].In CRC, western blot and immunohistochemistry (IHC) investigations identified the 57%–100% of samples have c-Met expression at the protein levels and messenger RNA (mRNA), while RT-PCR and northern blot analyses detected it in 30%–91% of samples [54]. According to recent studies, angiogenesis, metastasis, and tumor invasion are all regulated by the exact relationship between HGF and c-Met. Tyrosine kinase of the c-Met receptor controls how cancers develop.

The pie chart illustrates the proportion of new cancer cases across several types, each known to express both VEGFR and c-Met receptors as shown in Fig. 3. Breast cancer leads with 26% of the new cases in women worldwide, with over 2.3 million new cases in 2020, and aggressive overexpress these receptors. Presently, colorectal cancer ranks third in incidence worldwide, accounting for roughly 1.9 million new cases (21%) every year, and both VEGFR and c-Met are involved in its progression. The most prevalent form of lung cancer is non-small cell lung cancer (NSCLC), which makes up around 85% (2.1 million new cases, or 24%) of all instances of lung cancer, with significant overexpression of both VEGFR and c-Met. Gastric cancer accounts for 11% with around 1 million new cases annually, and often shows elevated levels of these receptors. At the same time, hepatocellular carcinoma (HCC) represents 9% (866,136 new cases).

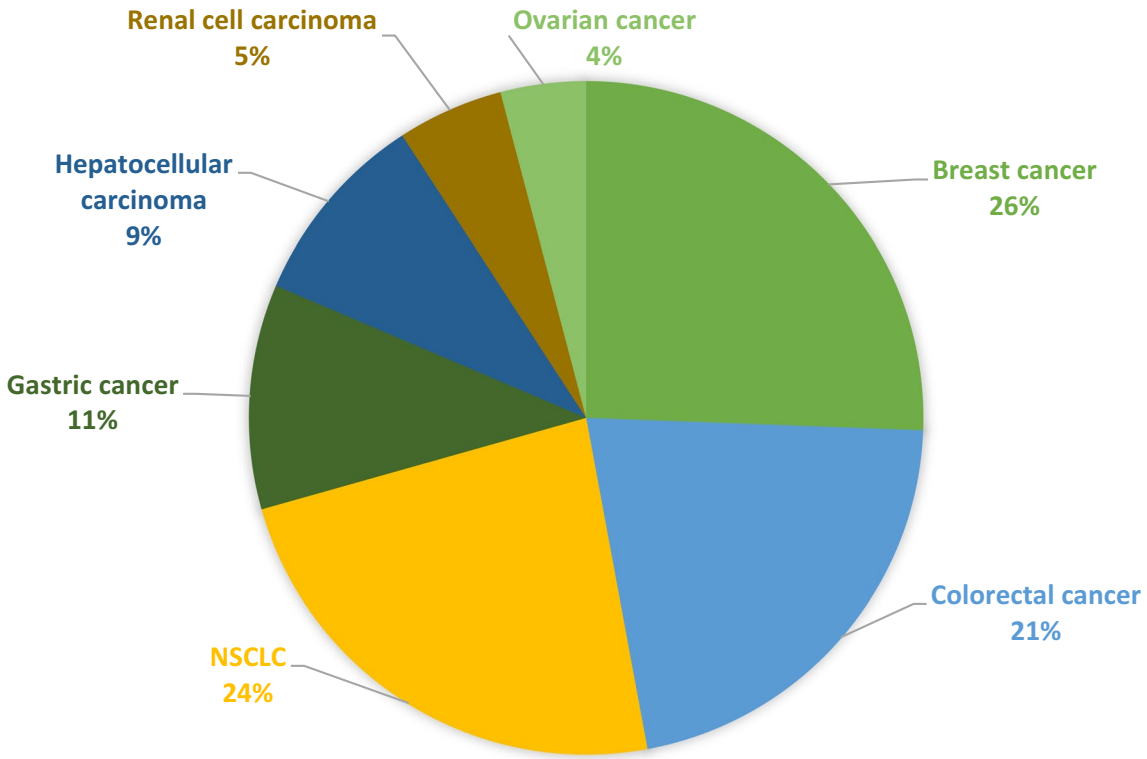


Fig. 3 The pie chart illustrates the proportion of new cancer cases across different types of cancers

Renal cell carcinoma contributes to 5% of the new cases, and ovarian cancer has the smallest share at 4%. This distribution highlights the varying prevalence of these cancers and the significant role of VEGFR and c-Met receptors in their progression.

The effectiveness and safety profile of cabozantinib, a dual inhibitor of MET receptor tyrosine kinase and vascular endothelial growth factor receptor (VEGFR), have been demonstrated by numerous clinical trials conducted on a range of cancer types. The phase III METEOR trial evaluated cabozantinib and Everolimus in patients with renal cell carcinoma who had previously undergone antiangiogenic treatment. The trial showed that cabozantinib improved overall survival (OS) (21.4 vs. 16.5 months), objective response rates (ORR) (17% vs. 3%), and progression-free survival (PFS) (7.4 vs. 3.8 months). Common adverse events included hypertension, diarrhea, fatigue, and hand-foot syndrome, managed with dose modifications and supportive care [55]. In metastatic castration-resistant prostate cancer (mCRPC), cabozantinib was evaluated in the phase III COMET-1 and COMET-2 trials. COMET-1 compared cabozantinib to prednisone in patients who had progressed after docetaxel, demonstrating improved radiographic PFS (5.6 vs. 2.8 months) and OS (11.0 vs. 9.8 months). COMET-2 explored cabozantinib in chemotherapy-naïve patients, showing benefits in PFS and OS. Adverse events included similar manageable side effects [56, 57].

The phase III CELESTIAL trial evaluated cabozantinib for hepatocellular carcinoma (HCC) in individuals who had previously received sorafenib. Results showed prolonged OS (10.2 vs. 8.0 months) and PFS (5.2 vs. 1.9 months) compared to placebo, with common adverse events such as hypertension, diarrhea, and fatigue [58]. In medullary thyroid cancer (MTC), cabozantinib's efficacy was demonstrated in phase II trials targeting RET mutations, showing significant tumor response rates and disease stabilization, leading to its approval for this indication [59]. Overall, cabozantinib's dual inhibition of VEGFR and MET has consistently shown efficacy in disrupting tumor growth and angiogenesis pathways across various cancers. The safety profile includes manageable adverse events commonly associated with tyrosine kinase inhibitors.

Dual VEGF and c-MET receptor inhibitors

The inhibition of c-Met and VEGFR could be effective in the treatment of cancers, both agents are typically used as monotherapy, and the effectiveness is often interfered by the development of drug resistance. Also, as different types of cancer exhibit different gene alterations and these alterations may differ from patient to patient, personalized medicine that can target both HGF independent and VEGF dependent pathways in a highly specific manner would be required for a better clinical outcome as shown in Fig. 2. Also, an agent that is effective in targeting cancer stem cells, which are believed to be the cause of tumorigenesis, and inhibiting metastasis and endothelial cells would make a "dual-inhibition" therapy even more promising in the fight against cancers in the future. There are various small molecules of VEGFR and c-Met inhibitors for the prevention and treatment of cancer.

Quinolones molecule

The ability of the quinolone molecule to inhibit several various tyrosine kinase receptors, including as VEGFRs, FGFR, PDGFR, c-Met, EGFR and c-Kit, has long aroused interest [60, 61]. Among them, quinolone derivatives which specially target dual VEGFR and CMET receptors are potent anticancer compounds.

- Cabozantinib

An oral multi-kinase inhibitor is called cabozantinib. The primary targets are MET, RET, AXL, and VEGFR2, receptor tyrosine kinases that are essential for tumor angiogenesis and the development of cancer cells. The FDA-approved drug cabozantinib, which is used to treat progressive, metastatic medullary thyroid carcinoma, is active in preclinical models of several cancers [62]. Due to their association to tumor progression, members of the signaling pathways for MET and VEGF are crucial targets in the advancement of medications targeting cancer treatment [63]. The cabozantinib, dual inhibitor of VEGFR2 and MET was discovered to have strong anticancer efficacy in a preclinical tumor xenograft model obtained from cancer patients [64–66].

- Foretinib

In gastric cancer, foretinib, an oral multi-kinase inhibitor, is known to target the VEGFRs, MET, RON, and AXL receptors. This compound was discovered by Exelixis and further development carried by Glaxo Smith Kline. Foretinib suppresses the cellular processes that result in extracellular signal-regulated kinase and Met phosphorylation in response to HGF and VEGF, respectively, and it stops tumor cells from responding to HGF and endothelial cells from responding to HGF/VEGF. Studies conducted in vitro showed that foretinib suppressed both Met and VEGFR-2 receptors, having half-maximal inhibitory concentration (IC50) values of 0.4 nM and 0.9 nM, respectively. Foretinib inhibits other receptors also like Flt-4, Flt-1, and RON with respective IC50 values of 6.8, 3, and 2.8 nM.

Administering a single oral dose of Foretinib at 100 mg/kg to mice for 24 h without fur led to a decrease in the phosphorylation of both c-Met and VEGFR-2 receptors in the liver and lungs, respectively, in vivo. The Phase II study of Foretinib was completed in 2017 [67–71].

- Pamufetinib

Pamufetinib also known as TAS-115, chemically is 4-[2-fluoro-4-[[[(2-phenylacetyl) amino]. thioxomethyl]. amino]. -phenoxy]. -7-methoxy-N-methyl-6-quin-olinecarboxamide, a new inhibitor of the kinases that are specifically aimed at the MET and the VEGFR with improved safety characteristics. In deficient cells MET or VEGFR signals, TAS-115 only moderately inhibited proliferation (GI50 > 10 M). The inhibitory impact of TAS-115 on VEGFR2 and MET equivalent to that of comparable kinase inhibitors targeting VEGFR and MET, as shown by their respective IC50 values of 0.030 and 0.032 mmol/L, such as sunitinib, crizotinib, and sorafenib. Based on these findings, TAS-115 demonstrates a high level of selectivity and specificity, particularly in vitro. When administered daily for six weeks in vivo tests, TAS-115 entirely stopped the growth of tumors with MET inactivation by preventing angiogenesis without causing any harm, even at serum saturation doses. From these results, it can be inferred that TAS-115 is a recently developed inhibitor that targets VEGFR/MET, showing enhanced effectiveness against cancer and reduced levels of toxicity [72–75]. TAS-115 is currently under the phase-1 clinical trial (Fig. 4).

A. Quinazoline molecule

- [1, 4]. dioxino[2,3-f]. quinazoline

Several variations of [1, 4]. dioxino[2,3-f]. quinazoline was synthesized to develop reversible and non-covalent dual inhibitors targeting both c-Met and VEGFR-2. By performing Kinase-Glo luminescent kinase assays, all newly synthesized compounds named as 7a-m were tested toward the VEGFR-2 receptor. To find out their inhibitory potential against c-Met, compounds 7a, 7 m, 7 k and 7 l having strong VEGFR-2 inhibitory activity was chosen. The nanomolar range for IC50 values, the enzyme assay revealed that the majority of the target compounds possessed inhibitory potential on VEGFR-2 as well as c-Met, particularly compounds 7 m and 7 k. Due to additional in vitro cell proliferation assays, compound 7 k effectively inhibited tumor growth in vivo in a mouse model of hepatocellular carcinoma (MHCC97H cells). There were good yields of the derivatives developed and 13C NMR, 1H NMR, and HRMS were used to elucidate the compound's structures. On MHCC97H and HUVEC cells, 7 m demonstrated even more potent antiproliferative effects than cabozantinib. Docking of the 7 m molecule with the kinase's enzyme of VEGFR-2 and c-Met, it was discovered that the [1, 4] dioxino of the molecule was bound to the receptor, making the complex the most stable [76].

- N-(2-(4-Fluorophenyl)-1H-benzo[d]. imidazol-6-yl) quinazolin-4-amine

This study synthesized and identified a series of N-(2-phenyl-1H-benzo[d]. imidazol-5-yl) quinazolin-4-amine derivatives against the c-Met & VEGFR-2 as a dual inhibitor. All of the synthesized derivatives of molecule quinazolin-4-amine fused with a benzimidazole group (7a–7u)

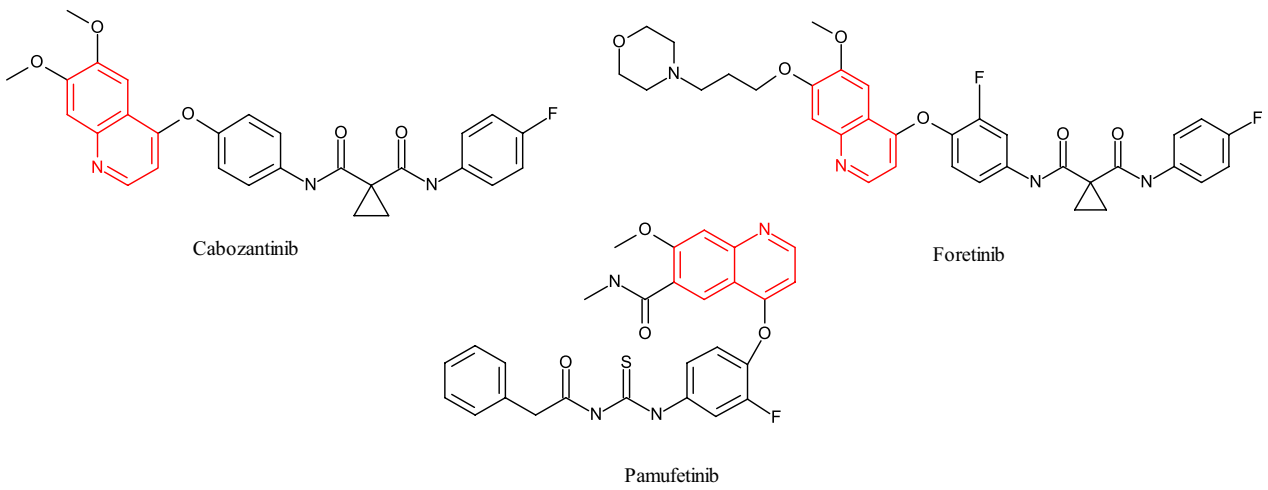


Fig. 4 VEGFR and c-MET inhibitor containing Quinolone ring

were subjected to evaluation. Compound 7j showed the highest activity among these compounds, with half maximum inhibitory concentrations (IC50) of 0.05 lm for the c-met and 0.02 lm for the vegfr, respectively. This is similar to golvatinib, which exhibits an IC50 of 0.02 μM for c-Met and 0.04 μM for VEGFR-2. By performing antiproliferative assay, compound 7j, which had the strongest the suppression activity of targeting c-Met/VEGFR-2, also displayed the strongest activities as anticancer agent, with IC50 values of HepG-2 and MCF-7, respectively, 1.5 lM and 8.7 lM. The most effective inhibitor 7j was molecularly docked into the sites on VEGFR-2 and c-Met that bind ATP, and the results revealed that the functional regions within the c-Met and VEGFR-2 kinases may be effectively bound by compound 7j. From all these results, concluded that compound 7j was a potential anticancer agent [77].

- Quinazoline-2,4(1H,3H)-dione

Hassan, A. et al. derived new 3-substituted quinazoline-2,4(1H,3H)-dione derivatives acting as dual inhibitors for c-Met/VEGFR-2 TK. They introduced novel synthetic approaches for previously reported derivatives (2a–g) and synthesized additional derivatives (3 and 4a–j). Among these, compounds 2c, 4b, and 4e exhibited significant inhibition against both c-Met and VEGFR-2 TK (with IC50 range of 0.052–0.084 mM). Compounds 4b and 4e displayed hydrogen bonding (HB) interactions with Asp1222 in the HB region of c-Met TK. For VEGFR-2 TK, compound 4b formed HB with Asp1046, while compound 4e formed HB with Glu885 and Asp1046. Additionally, they conducted in silico prediction of pharmacokinetic and physicochemical properties using the SwissADME website. These quinazoline-2,4(1H,3H)-dione derivatives show promise as antiproliferative agents, but further optimization is necessary [94].

- 3-phenylquinazolin-2,4(1H,3H)-diones

Hassan A et al. reported a new series of 3-phenylquinazolin-2,4(1H,3H)-diones containing a thiourea group as dual inhibitors of VEGFR-2 and c-Met TKs. Depending on the pharmacophore of cabozantinib novel dual inhibitors of VEGFR-2 and c-Met TKs and synthesized them using a new single-pot three-component reaction. We evaluated the cytotoxic effects of these synthesized compounds on the HCT-116 colorectal cancer cell line. Compounds 3c and 3e demonstrated the most potent cytotoxicity against the HCT-116 cell line (with IC50 values of 1.184 and 3.403 μM, respectively). Furthermore, we assessed the in vitro enzyme inhibitory activity against both VEGFR-2 and c-Met TKs. Compound 3e exhibited the highest inhibitory activity against both VEGFR-2 and c-Met (with IC50 values of 83 and 48 nM, respectively). Docking studies revealed that the α-oxo group in the quinazoline ring formed a hydrogen bond with the Met1160 residue in the adenine region of c-Met TK [93] (Fig. 5).

B. Pyridine molecule

- Golvatinib (E7050)

In order to block both c-Met and the VEGFR)-2, we developed the novel, orally active small molecule Golvatinib (E7050), N-[2-Fluoro-4-({2-[4-(4-methylpiperazin-1-yl)piperidin-1-yl].carbonylaminopyridin-4-yl} oxy)phenyl].-N′-(4fluorophenyl) cyclopropane-1,1-dicarboxamide. Studies conducted in vitro show that E7050 has a strong inhibitory effect on the phosphorylation of VEGFR-2 and also c-met. Golvatinib (E7050) also effectively prevents the development of cells induced by either VEGF/HGF as well as c-met amplified tumor cells. E7050 was used in in vivo investigations that demonstrated that prevention of tumors' growth as well as phosphorylation of both receptors and angiogenesis of tumors in xenograft models. Our results show that E7050, a powerful dual inhibitor targeting both VEGFR-2 and c-Met, has therapeutic efficacy in the fight against cancer. E7050 is presently being assessed in a phase II clinical investigation in accordance with our preclinical justification [78–81].

- N- [4-({2- [(Cyclopropyl carbonyl) amino]. imidazole[1,2-a]. pyridin-6-yl} oxy)-3-fluorophenyl]. -6-methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carboxamide hydrochloride

In this study, Matsumoto S et al. designed and synthesized molecules (inhibitors) with para-substitution from the VEGFR2 and c-Met complex kinases with association of known inhibitors by using structural co-crystal data to generate unique molecule as dual inhibitor (c-Met and VEGFR2). Pyrazolines and pyridine derivatives were created through additional optimization; these compounds could generate hydrogen bonds(intramolecular) that enforced rigidity in conformity and led to effective inhibition. A notable molecule to highlight is the derivative (26) of imidazo[1,2-a]. pyridine featuring a 6-methylpyridone ring. This compound notably restricted the activities of VEGFR2 and c-Met enzymes (with IC50 values of 1.9 and 2.2 nM, respectively), along with inhibiting the growth of MKN45 cells, which rely on c-Met, and human umbilical vein cells stimulated by VEGF (with IC50 values of 5.0 and 1.8 nM, respectively). In mice xenograft

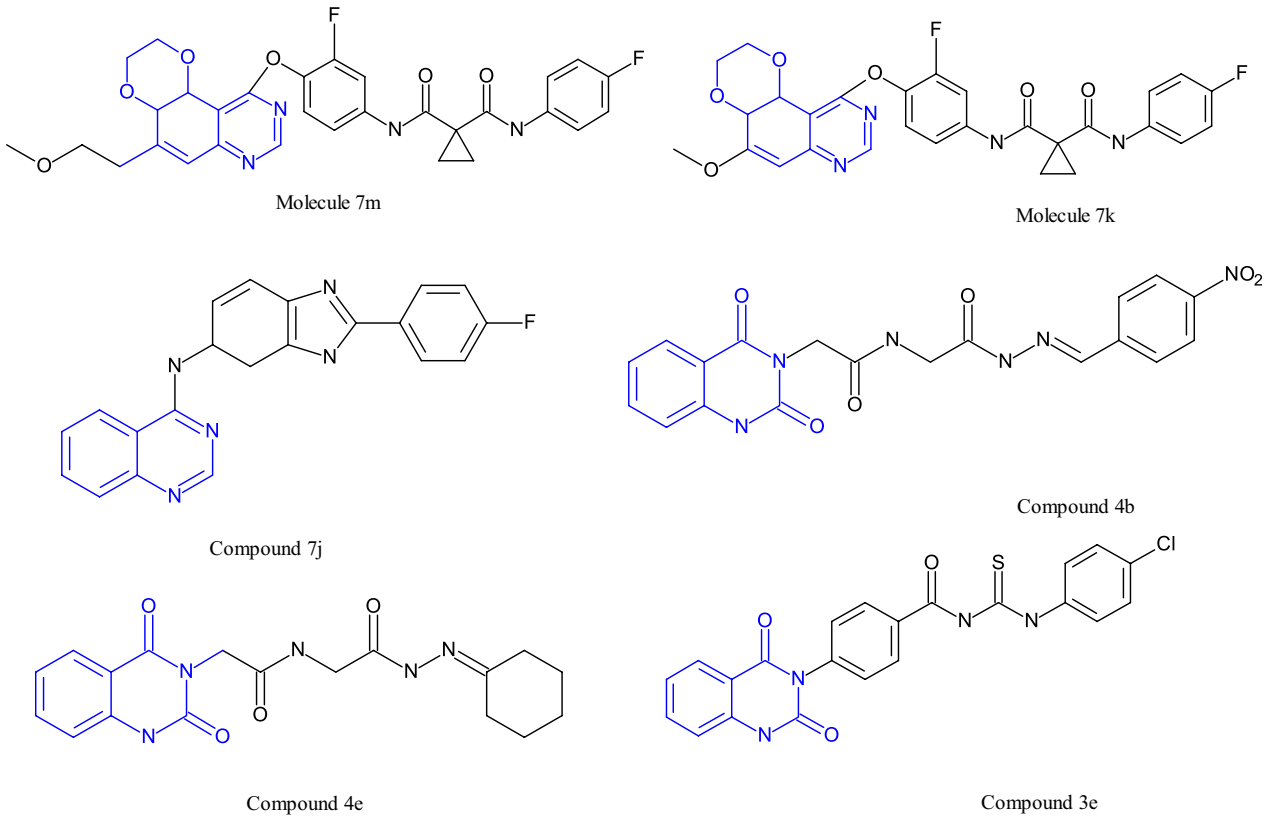


Fig. 5 VEGFR and c-MET inhibitor containing quinazoline ring

models, compound 26 showed anticancer efficacy in vivo which is dose-dependent on MKN45 and COLO205 cells with 4% and 13% (treated/control ratio) [T/C], respectively. According to our research, the therapeutic potential of compound 26 for the treatment of human cancer is promising [82].

- BMS-794833

A new, powerful VEGFR-2/c-Met dual inhibitor, BMS-794833, has an IC50 of 1.7 nM/15 nM. By obstructing cell movement and scattering and the phosphorylation of downstream signaling pathways, BMS-794833 blocked Met property. BMS-794833 inhibits the growth of tumors in the GTL-16 gastric cancer model by more than 50% for at least one period equivalent to the tumor doubling time. When given once daily for 14 days, none of the dose levels show any signs of toxicity. After oral treatment, the BMS-794833 molecule showed efficacy as an antitumor agent in vivo with dose-dependent property and no toxicity by using the xenograft model of L2987 and GTL-16 cells (lung carcinoma). Consequently, BMS-794833 might be an effective anti-angiogenic drug as a result of its dual potential [82, 83].

- 2-substituted-4-(2-fluorophenoxy) pyridine

The design and synthesis of a 2-substituted molecule derivatives 4-(2-fluorophenoxy) pyridine. The in vitro cell proliferation assay showed that many target compounds, particularly compounds 9 h, 12b, and 12d, had potent inhibitory effects on both kinase receptors such as VEGFR-2 and c-Met. Compound 12d exhibited activity against c-Met and VEGFR-2 in vitro enzyme assays, with IC50 values of 0.11 μM and 0.19 μM, respectively, was thought to be the most potential compound. Further molecular docking research revealed that VEGFR-2 and c-Met shows a similar binding interactions mechanism at ATP-binding site, indicating that 12d might be an effective cancer treatment medication. Compound 12d demonstrated the strongest inhibiting actions on the BaF3-TPR-Met cell which having 0.13 lM IC50 value and HUVEC cells have 0.30 lM value. Regarding VEGFR-2 kinase receptors and c-Met, particularly compound 12d showed more enzymatic efficacy than other compounds with 0.11 lM and 0.19 lM (IC50 values), respectively. These findings showed that a viable molecule for further research is compound 12d being a strong dual inhibitor of VEGFR-2 and c-Met kinase enzymes [84] (Fig. 6).

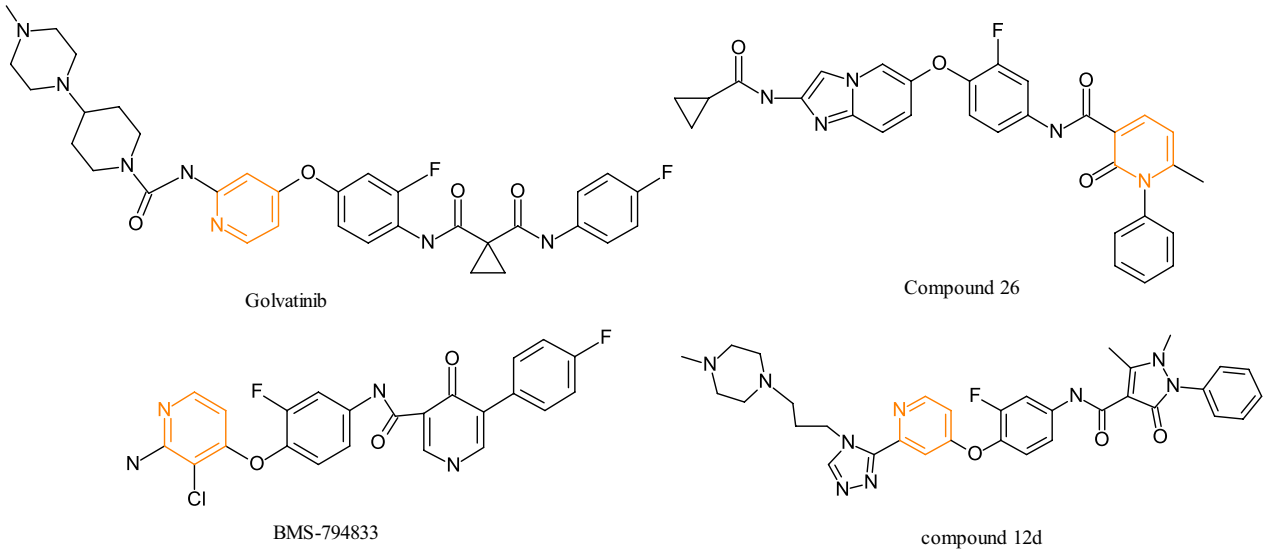


Fig. 6 VEGFR and c-MET inhibitor containing pyridine ring

C. Pyrimidine molecule

- Thieno[2,3-d]. pyrimidine

A group of very effective thieno[2,3-d]. pyrimidine-containing dual inhibitors of VEGFR-2 as well as c-Met. The cell proliferation assay designated the most potential molecules by in vitro process, particularly compounds 12j and 12 m, were in the nanomolar range for IC50 values and had inhibitory efficacy on the kinase receptors c-Met and VEGFR-2. Compound 12j was determined to be the most effective one depending on the additional in vitro enzyme assay; its IC50 values for c-Met and VEGFR-2 were 25 nM and 48 nM, respectively. The strong inhibitory actions of compound 12j were demonstrated against HUVEC and BaF3-TPR-Met, which had values of IC50 at 0.051 lM and 0.086 lM, respectively. Then, molecule 12j was docked with the c-Met and VEGFR-2 both kinase receptors, and the structural activity of these analogues was analyzed. All of the findings point to the potential of 12j as a dual inhibitor. As a result, we concluded that the 4-fluoro-phenyl-cyclopropane-1,1-dicarboxamide and thieno[2,3-d]. pyrimidine moieties of the analogues were crucial for their efficiency against c-Met and VEGFR-2 [85].

- 4-Aminopyrimidine-5-cabaldehyde oximes

Qiang H. et al. discovered novel dual inhibitor, which synthesized several derivatives that contain powerful dual inhibitors such as 4-Aminopyrimidine-5-cabaldehyde oxime scaffold. In vitro, the cell proliferation assay having IC50 values revealed that the majority of targeted molecules have potent inhibitory potential on both c-Met and VEGFR-2. Compound 18a was thought to be the most effective one according to the additional in vitro enzyme assay; its IC50 values for c-Met and VEGFR2 were 210 nM and 170 nM, respectively. According to all the findings, 18a is a dual inhibitor of kinase enzymes with promising future. Our results suggested that compound 18a might serve as a potent compound for the development of a dual inhibitor of VEGFR2& c-Met [86].

- Anilinopyrimidine

Zhan Z. et al. revealed a group of highly effective anilinopyrimidine-based dual c-Met and VEGFR-2 enzyme inhibitors. At the enzymatic level, certain analogues showed nanomolar efficacy against these enzymes. The compounds 18a, 3a, 3b, 3 g, and 3 h showed a strong action as antiproliferative with IC50 values ranging from 0.33 to 1.7 M against c-Met addicted cell lines. The favored compounds 18a and 3 g also showed strong antiproliferative effects in various cancer cells such as MKN-45, EBC-1, c-Met phosphorylation suppression and EBC-1 associated signaling pathways in cells, besides their enzymatic property. Most potent dual inhibitors (c-Met/VEGFR-2) will be developed with the use of SARs that inhibit c-Met/VEGFR-2 [87].

- Benzylidene-6-(5-chloropyrimidin-2-yl)-9H-purine-2,6-diamine

More S. et al. developed unique series of benzylidene-6-(5-chloropyrimidin-2-yl)-9H-purine-2,6-diamine

derivatives with the aim of inhibiting angiogenesis. Among these derivatives, SM-6 demonstrated promising anticancer properties and underwent assessment for its potential to inhibit enzymes in vitro using a flow cytometer. Additionally, it prompted apoptosis and halted the cell cycle at the G0/G1 phase in HT-29 cells, as evidenced by DAPI and propidium iodide (PI) staining followed by flow cytometry analysis. While these compounds displayed modest inhibitory effects on VEGFR and c-Met kinases, further investigation of their active structures is warranted, which could positively contribute to the development of small anticancer inhibitors targeting both VEGFR and c-Met kinases [95] (Fig. 7)

C. Pyrazine molecule

In the exploration of dual inhibitors, a range of novel [1, 2, 4]. triazolo [4,3-a]. pyrazine derivatives were developed and assessed in vitro for their ability to inhibit cell proliferation and c-Met/VEGFR-2 kinases. Among these, compound 17 l emerged as the most promising, exhibiting significant kinase inhibition (c-Met IC50 = 26.00 nM and VEGFR-2 IC50 = 2.6 M) and demonstrating notable antiproliferative effects against A549, MCF-7, and Hela cancer cell lines (IC50 values of 0.98 0.08, 1.05 0.17, and 1.28 0.25 M, respectively). In silico study revealed that, like foretinib, compound 17 l effectively interacts with c-Met and VEGFR-2 proteins. Therefore, for the development of potent anticancer therapies, further investigation of compound 17 l as a potential dual c-Met/VEGFR-2 inhibitor [88] (Fig. 8)

E. Oxindole moiety

- 5-Methoxy-3-(2-(6-phenyl-7H- [1, 2, 4]. -triazolo[3,4-b].—[1, 3, 4]. -thiadiazin-3-yl)-hydrazineylidene)-indolin-2-one

The many derivatives of 3-(triazolo-thiadiazin-3-yl)-indolin-2-one (6a-y) serve as dual inhibitors. The anticancer activities of representative molecules such as6b,6a, 6 l, 6n,6v, 6r, 6e and 6y were examined toward the human cell line NCI 58 at 10 M concentration by utilizing in vitro screening test (single-dose).The effective antiproliferative compound was compound 6b,

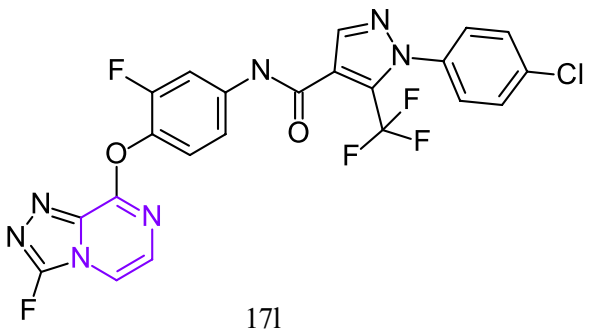


Fig. 8 VEGFR and c-MET inhibitor containing pyrazine ring

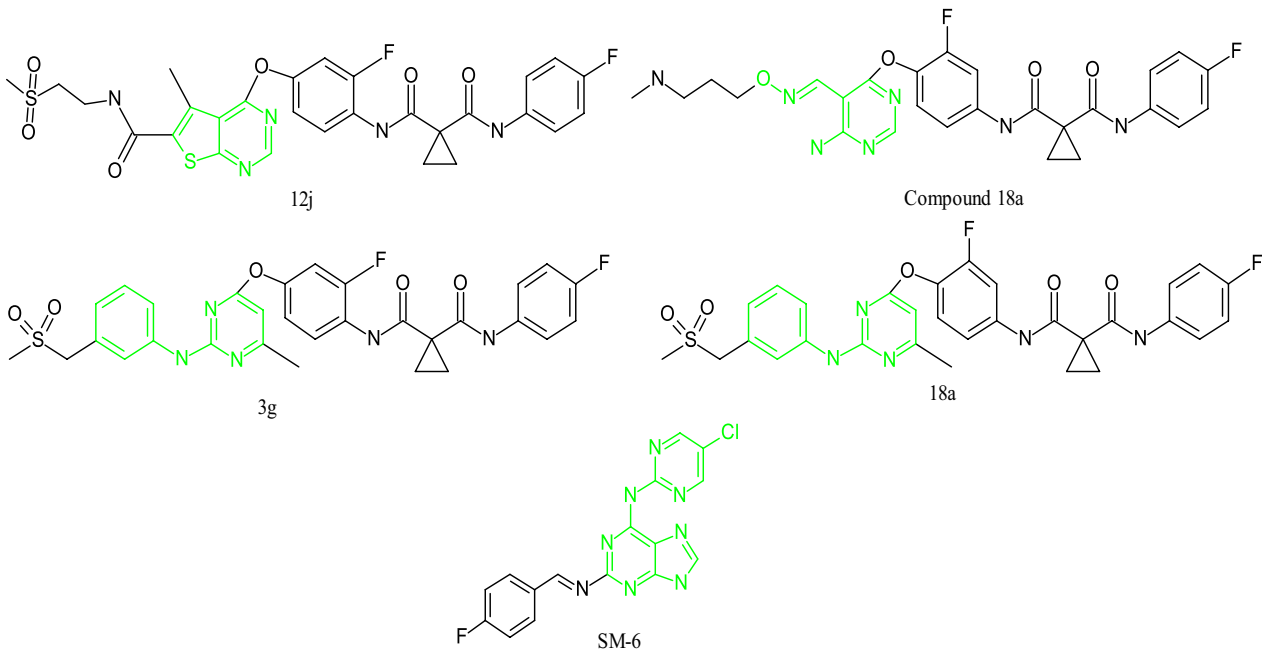


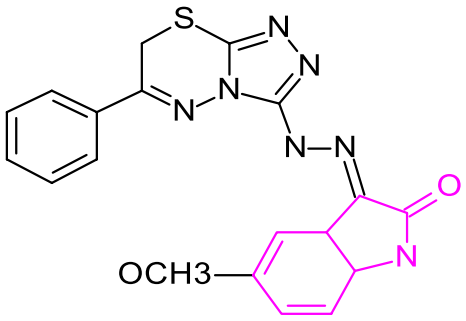
Fig. 7 VEGFR and c-MET inhibitor containing pyrimidine ring

which having broad-spectrum efficacy against various no. of cell lines from several subpanels of cancer. The most potent analogue, compound 6b, showed an average of 40% growth inhibition against ovarian cancers, leukemia, NSCLC, colon, and prostate cancers between 51 and 85%. In inhibitory experiments for both receptors C-Met and VEGFR-2 kinase, compound 6b demonstrated IC50 values of 371,435, and 654 nM, respectively, indicate inhibitory effects at sub-micromolar concentrations. The oxindole moiety's critical function in compound 6b's docking within the active sites of both kinase receptors was demonstrated by the hydrogen bonds that were discovered that c-Met kinase receptor at Met1160 amino acid and VEGFR2 active site with D1222, respectively [89] (Fig. 9)

F. Triazine derivatives

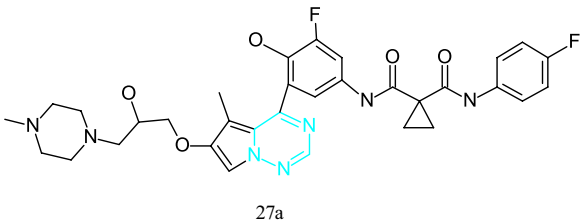
- Pyrrolo-[1,2-f].—[1, 2, 4]. triazine

A derivative of pyrrolo-[1,2-f].—[1, 2, 4]. triazine compounds were developed and manufactured to produce powerful inhibitor of VEGFR-2and c-Met. In-depth research revealed, 27a had optimum inhibitory effect toward VEGFR-2 receptor at IC50 value 5.0 ± 0.5 nM and with c-Met receptor having 2.3 ± 0.1 nMIC50 value, respectively. The lowest binding energy of the docking complex is reliable by analyzing the binding mechanism of compound 27a complex. The half maximum inhibitory concentration (IC50) against the BaF3-TPR-Met having 0.71 ± 0.16 nM which is more advantageous than positive compound and HUVEC-VEGFR2having 37.4 ± 0.311 nM which is equal to the positive compound, it also demonstrated the best anticancer activity, which is by those of cancer cell lines which are c-Met sensitive. All evaluation trials collectively suggested that molecule 27a might be a potential anticancer agent that deserved further investigation [90] (Fig. 10)



6b

Fig. 9 VEGFR & c-MET inhibitor containing oxindole ring



27a

Fig. 10 VEGFR and c-MET inhibitor containing triazine ring

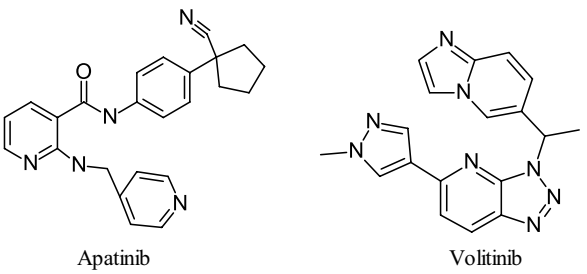
Combination of VEGFR and CMET Inhibitors

- Apatinib + volitinib:

For the effective action of inhibitors, we examined in vivo assay of combination therapy of the antitumor agent volitinib (c-Met inhibitor) and apatinib as anti-VEGFR agent by utilizing xenograft mouse model (CRC patient-derived). Among the two PDX models, this combined therapy greatly slowed the growth of tumors. While alone therapy of volitinib shows slightly improved tumor growth prevention, combined treatment in PDX models produced a synergistic decrease in micro-vessel density, suppression of proliferation, and increase in apoptosis [91] (Fig. 11)

- Pazopanib + tivantinib

The growth factors known as vascular endothelial growth factor and hepatocyte growth factor signaling pathways combine to promote angiogenesis. Using 32 patients with resistant solid tumors, we performed clinical trials (Phase 1) of the combination of pazopanib as VEGFR-targeting entity and tivantinib as c-MET receptor inhibitor at 5 dose levels to verify the pharmacokinetics and pharmacodynamics properties of the compound with determining safety as well as toxicity. In that clinical trial, patients got either combination (pazopanib + tivantinib) at escalation phase (from starting of therapy) or pazopanib alone medication with tumor pair sampling



Apatinib Volitinib

Fig. 11 Combination of apatinib + volitinib as Vegfr and c-met inhibitor

for seven days. Of the 31 evaluable patients, 20 had a stable illness that lasted up to 22 cycles [92] (Fig. 12)

Significance of dual inhibitors VEGFR2 and c-MET

Dual inhibitors targeting VEGFR2 and c-MET hold significant promise in advancing cancer therapy by addressing critical mechanisms involved in tumor growth, angiogenesis, and metastasis. By simultaneously inhibiting both VEGFR2 and c-MET, dual inhibitors can disrupt these interconnected pathways, thereby exerting a more comprehensive anti-tumor effect [96]. This dual targeting approach not only impedes the tumor's ability to sustain its blood supply and growth but also inhibits mechanisms that promote metastasis, potentially leading to improved overall survival rates for patients. Additionally, dual inhibitors offer the potential to overcome resistance that often develops with monotherapies targeting only one pathway [97]. Tumors that evade VEGFR2 inhibitors through compensatory activation of c-MET, or vice versa, can be effectively targeted by a dual inhibitor, thereby reducing the likelihood of therapeutic resistance and relapse. This makes dual inhibitors a promising strategy for achieving sustained tumor control. Moreover, their broad applicability across various cancer types, particularly those exhibiting dysregulation of both VEGFR2 and c-MET, highlights their potential to benefit a wide range of patients.

Challenges and limitations of dual inhibitors

The development and clinical application of dual inhibitors targeting VEGFR2 and c-MET face significant challenges and limitations. One primary challenge is the increased toxicity resulting from the simultaneous inhibition of these two critical signaling pathways. Both VEGFR2 and c-MET are involved in essential physiological processes such as angiogenesis, cell proliferation, and tissue regeneration, and their dual inhibition can lead to severe side effects, including cardiovascular complications, gastrointestinal issues, and impaired wound healing [98]. These adverse effects necessitate careful dose optimization and stringent patient monitoring to balance therapeutic benefits with patient safety. Additionally, the heterogeneity of tumor biology means that not all patients may benefit equally from dual inhibition. Tumors can vary widely in their reliance on VEGFR2 and c-MET signaling, making it essential to identify predictive biomarkers that can help select patients who are most likely to respond to such treatments.

Another critical limitation is the potential development of resistance mechanisms. Tumors are adept at adapting to targeted therapies by activating alternative signaling pathways or acquiring mutations that render the inhibitors ineffective. This adaptive resistance can diminish the long-term efficacy of dual inhibitors, necessitating the development of combination strategies or second-line therapies to sustain treatment benefits [99]. Furthermore, the complexity and cost associated with the development, clinical testing, and regulatory approval of dual inhibitors pose significant financial and logistical barriers. Extensive preclinical studies and multiple phases of clinical trials are required to establish the safety and efficacy of these agents, contributing to the high costs and lengthy timelines of bringing dual inhibitors to market. Despite these challenges, ongoing research is focused on improving the safety profiles, identifying robust biomarkers for patient selection, and developing combination approaches to enhance the overall effectiveness of dual VEGFR2 and c-MET inhibitors in cancer therapy.

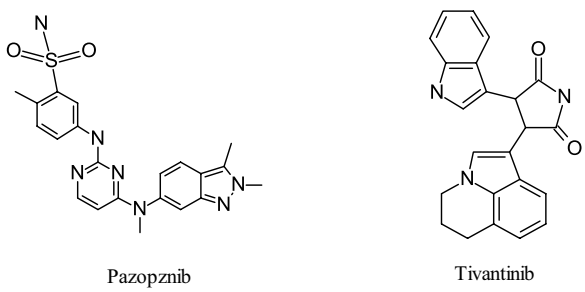


Fig. 12 Combination of pazopanib + tivantinib as Vegfr and c-met inhibitor

Implications for future research

From a clinical practice perspective, the use of dual inhibitors could lead to more personalized and effective cancer treatments, particularly for patients with tumors that exhibit high activation of both VEGFR2 and c-MET pathways. The development of robust biomarkers will be crucial in identifying patients who are most likely to benefit from these therapies, optimizing treatment plans, and improving prognostic accuracy. Future research implications include the need for extensive studies to refine the safety profiles of these inhibitors, as managing increased toxicity remains a challenge. Researchers will also need to explore combination strategies that incorporate dual inhibitors with other therapeutic modalities, such as immunotherapy or chemotherapy, to maximize treatment efficacy and minimize resistance. Overall, the advancement of dual VEGFR2 and c-MET inhibitors holds promise for more effective and durable cancer treatments, potentially transforming the therapeutic landscape and offering new hope for patients with aggressive and resistant cancers.

Conclusion

According to the most recent research, the US FDA has approved several anticancer agents for various cancer types. Different targets and signaling pathways are available in cancer to prevent the disease or treat it therapeutically. Specifically, the c-Met protein, known for its role in mesenchymal–epithelial transition, and the receptor for vascular endothelial growth factor play vital roles in cancer therapy. While some anticancer drugs had drawbacks like toxicities and resistance to treatment. Multi-target inhibition therapy has been effective in overcoming these drawbacks. For further development, various small molecule derivatives have been designed and synthesized in recent years for dual VEGFR and CMET inhibition. In this review, we summarize various molecules that developed as dual inhibitors of VEGFR and c-MET such as quinolones and quinazolines derivatives, pyridine and pyrimidine derivatives, oxindole moiety and triazine derivatives. Clinical trials are currently being conducted on a few of them while are being under investigation. The therapeutic efficacy and potency of molecules are also enhanced by some combination therapies, including apatinib + volitinib and pazopanib + tivantinib (currently under clinical trials). VEGFR and c-MET inhibitors as dual inhibitors may be more significant in future clinical anticancer treatments.

Abbreviations

VEGFR	Vascular endothelial growth factor receptor
RTKs	Receptor tyrosine kinases
NRTKs	Non-receptor tyrosine kinases
TKI	Tyrosine kinase inhibitor
MET	Mesenchymal–epithelialtransition factor
HGFR	Hepatocyte growth factor receptor

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Author contributions

Sachin A. Dhawale contributed to the conceptualization, analysis, writing—original draft, supervision, methodology, reviewing, and editing. All co-authors have contributed equally.

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Availability of data and material

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The authors declare no conflict of interest.

Competing interests

The authors declare no competing interests.

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