RECENT ADVANCES IN DRUGS TARGETING PROTEIN KINASES FOR CANCER THERAPY.

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ABSTRACT

Cancer has continued to be utmost challenging and life-threatening diseases to treat. Worldwide, cancer has been proven to be a major cause of death after cardiovascular diseases. The development of new drugs that can be able to inhibit the proliferation of cancerous cells only with minimum or without any side effects on healthy cells is a quite challenging task. Protein kinases are enzymes located in the cytoplasm that phosphorylate proteins. Protein kinases mediate most of the signal transduction in eukaryotic cells and also control many other cellular processes, including metabolism, transcription, cell cycle progression, cytoskeletal rearrangement and cell movement, development, the immune response, nervous system function, apoptosis, and differentiation. Normally, the activity protein kinases are stringently regulated. However, under pathological conditions, deregulation of protein kinases can lead to altered kinase expression and functions, and the initiation and survival of tumors. Therefore, protein kinases are a very attractive target class for therapeutic interventions in many disease states such as cancer. Kinase inhibitors now account for a quarter of all current drug discovery research and development efforts. Therefore, researchers around the globe are involved in the development of more efficient and safer targeted kinase inhibitors.

Objectives

To complement the published literature on clinical kinase inhibitors, we have prepared a review that recaps this large data set into an accessible format for the medicinal chemistry community. Here, we review the remarkable progress made over the past 20 years in improving the potency and specificity of small-molecule inhibitors of protein for cancer therapy.

Results

In summary, the potential for developing novel types of kinase inhibitor is huge, and we confidently predict that this will continue to be a major growth area over the next 20 years,

Keywords: Protein kinase, cancer, EGFR, VEGFR, ABL, BTK, JAK inhibitors

Introduction

Reversible phosphorylation of proteins and lipids is a key component of many cellular signaling pathways including those involved in cell growth, differentiation, proliferation, angiogenesis, apoptosis, cytoskeletal rearrangement, and metabolism. The process of phosphorylation is mediated via the action of kinases (Kuhn 2010).

1.1. Protein kinases as drug targets

Kinase inhibitors now account for a quarter of all current drug discovery research and development efforts. Recent advances in the fundamental molecular mechanisms underlying cancer cell signaling have elucidated a crucial role for kinases in the carcinogenesis and metastases of various types of cancer (Köstler and Zielinski 2015). However, dysregulation of kinases has been demonstrated in many human disorders including immune, neurological and infectious diseases (Mueller, Mack et al. 2005, Sato, Sanjo et al. 2005, Chong, Shang et al. 2012, Tabit, Shenouda et al. 2013).

Kinase Inhibitors for cancer therapy

Most protein kinases promote cell proliferation, survival and migration, when constitutively overexpressed, or active, they are also associated with oncogenesis (Maurer, Tarkowski et al. 2011). Genetically inherited variants of specific kinases are causally linked to cancer development, promotion, progression and recurrence (Köstler and Zielinski 2015, Kittler and Tschandl 2018). Multiple human malignancies have been identified to be associated with modulation and dysfunction of protein and lipid kinases and deactivated phosphatases on account of chromosomal reshuffling and genetic mutations (Bartram, de Klein et al. 1983, Bardelli, Parsons et al. 2003, Futreal, Coin et al. 2004). Inhibition of the distinct kinase signaling pathways can be less cytotoxic to non-cancerous cells, thus presenting the selective killing of tumor cells with considerably lower toxic manifestations (Davies, Reddy et al. 2000, Druker, Guilhot et al. 2006). Due to improved clinical efficacy, U.S. Food and Drug Administration (FDA) has approved many small-molecule kinase inhibitors for clinical use. These kinase inhibitors include target kinome members such as EGFR, VEGFRs, ABL, BRAF, BTK, SRC and mTOR, all providing improved clinical outcome and patient health status (Fabian, Biggs et al. 2005, Köstler and Zielinski 2015).

TKI targeting epidermal growth factor receptor (EGFR)

Epidermal growth factor receptor (EGFR) is a trans-membrane glycoprotein, consisting of extracellular ligand-binding domain and cytoplasmic tyrosine kinase domain. EGFR belongs to a family of four related receptor tyrosine kinases and acts as a key mediator in cell signaling pathways including cell cycle progression, inhibition of apoptosis, angiogenesis, tumor cell motility and metastasis (Sharma, Bell et al. 2007, Ayati, Emami et al. 2019). The abnormal signaling of these pathways results in disregulated cell proliferation, evasion from apoptosis, angiogenesis, migration, and metastasis of cancer cells (Lemmon and Schlessinger 2010).

EGFR TK as a target for cancer treatment

In normal cells, the expression of EGFR ranges from 40,000 to 100,000 receptors per cell (Zimmermann, Zouhair et al. 2006). In contrast, EGFR is overexpressed in the majority of solid tumors, including breast, colorectal, prostate, kidney, pancreas, ovary, and brain, head-and-neck cancers, and non-small-cell lung cancer (NSCLC) (Wee and Wang 2017) leading to the disappointing treatment results by causing resistance to hormonal therapy, cytotoxic agents, and radiotherapy.

Epidermal growth factor receptor inhibitors

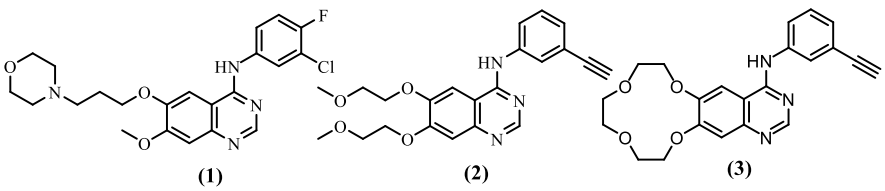
Inhibition of the oncogenic EGFR tyrosine kinase activity takes place by the use of small molecule tyrosine kinase inhibitors (EGFR TKIs). These small molecules inhibit EGFR signaling by competing and binding with ATP-binding pockets on the intracellular catalytic kinase domain of RTKs, thereby preventing autophosphorylation and activation of several downstream signaling pathways (Herbst 2004, Pytel, Sliwinski et al. 2009).

EGFR targeted tyrosine kinase inhibitors approved for cancer therapy.

To date, EGFR-TKIs are relatively in depth researched with four generations being developed (Huang, Jiang et al. 2020):

- **First-generation EGFR TKIs**

Geftinib **1** (Iressa®) (Mok, Wu et al. 2009, Mitsudomi, Morita et al. 2010), erlotinib **2** (Tarceva®) (Rosell, Carcereny et al. 2012) and icotinib **3** (Conmana®) (Shi, Zhang et al. 2013, Shi, Wang et al. 2017) are an anilinoquinazoline-derived first-generation EGFR TKIs that reversibly bind to the kinase domain of EGFR and potently inhibit the receptor when it has been constitutively activated by common mutations.. Gefitinib and erlotinib, also inhibit, to a lesser extent, wild-type EGFR ($EGFR^{WT}$) (Riely, Politi et al. 2006). Gefitinib and erlotinib have received approval from U.S Food and Drug Administration (FDA) for the treatment of advanced non-small cell lung cancers (NSCLCs) with activating epidermal growth factor receptor (EGFR) mutations (exon 19 deletions or L858R) in 2003 and 2004, respectively (Soria, Wu et al. 2015). Most initially respond to the EGFR tyrosine kinase inhibitors (TKIs) however, over time (median of 6-12 months), most tumors develop acquired resistance to EGFR TKIs as a result of EGFR-TK mutation, followed by disease progression (Pao, Miller et al. 2005, Nguyen, Kobayashi et al. 2009, Wang, Wang et al. 2016). These mutations decrease the binding of ATP-competitive inhibitor to the kinase and restores ATP affinity to EGFR (Kobayashi, Boggon et al. 2005), so these mutations are responsible for the resistant to currently available TKIs (Engel, Richters et al. 2015).



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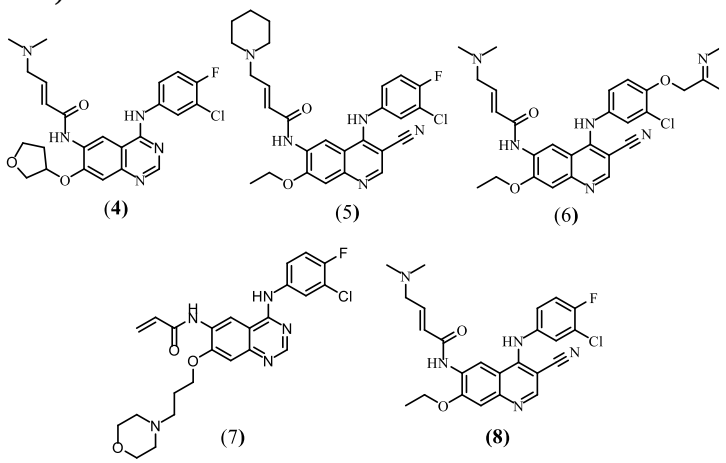
- **Second-generation EGFR TKIs**

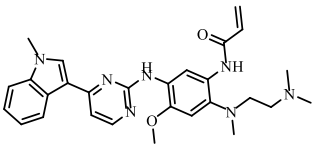
The development of second-generation EGFR TKIs was driven to overcome the drug resistance induced by EGFRT790M which comes from the failure of first-generation EGFR TKIs by simultaneously and irreversibly repressing different ErbB receptors. Several 4-anilinoquinazoline and 4-anilinoquinoline derivatives have been developed as second-generation EGFR TKIs, including afatinib **4** (Gilotrif®) (Ricciuti, Baglivo et al. 2018), dacomitinib **5** (Vizimpro®) (Lau, Batra et al. 2019), neratinib **6** (Nerlynx®) (Food and Administration 2017), Canertinib **7** (CI-1033) (Sachdev and Jahanzeb 2012), and pelitinib **8** (EKB-569) (Zang, Sohn et al. 2020). Most of such inhibitors comprises electrophilic acrylamide moiety as Michael-acceptor system that could form a covalent bond with Cys797 at the lip of the ATP binding cleft of EGFR causing the inactivation of the protein (Kwak, Sordella et al. 2005, Engelman, Zejnullahu et al. 2007, Li, Ambrogio et al. 2008).



- **Third-generation EGFR TKIs**

The third-generation EGFR TKIs, namely mutant-selective EGFR TKIs, showed promising efficacy in NSCLC patients whose illness is resistant to the first- and second-generation EGFR TKIs. Most of these inhibitors with amino- pyrimidine scaffold covalently bind to active thiols of Cys797 through their electrophilic acrylamide Michael-acceptors. This category of inhibitors selectively and irreversibly targeted mutant $EGFR^{T790M}$ over wild-type EGFR ($EGFR^{WT}$) (Cheng, Nair et al. 2016). Such agents as osimertinib **9** (Tagrisso®) [47], olmutinib **10** (HM61713) (Park, Jänne et al. 2021), WZ4002 **11** (Stasi and Cappuzzo 2014, Engel, Lategahn et al. 2016), and Rociletinib **12** (CO-1686) (Sequist, Soria et al. 2015) showed improved selectivity toward $EGFR^{T790M}$ over the $EGFR^{WT}$.

Despite the high efficacy of the third-generation EGFR TKIs, the progression of epigenetic mutation and acquired resistance have restricted the use of these inhibitors in clinical issues. EGFR C797S mutation was reported to be a leading mechanism of resistance to the third-generation inhibitors. The C797S mutation appears to be an ideal target for overcoming the acquired resistance to the third-generation inhibitors (Zhang, Guo et al. 2018).



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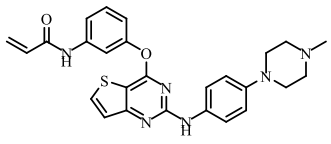

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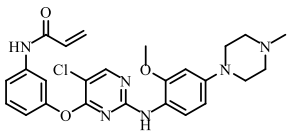

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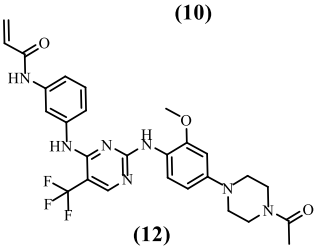

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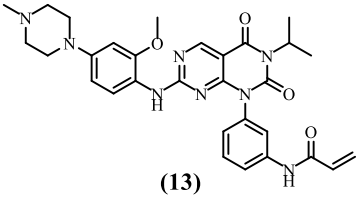
Recent mutant covalent EGFR^{T790M} inhibitors

a- Pyrimidinopyrimidine derivatives

A series of pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives as novel potent and selective EGFR$^{L858R/T790M}$ inhibitors were designed and synthesized. The most promising compound **13** demonstrated significant inhibitory activity and selectivity at both *in vitro* and *in vivo* levels, indicating that compound **13** might be used as a promising drug candidate to overcome EGFR$^{L858R/T790M}$ drug-resistance mutation (Hao, Lyu et al. 2018).

b- Aminopyrimidine-based derivatives

Some new 2-anilino-pyrimidine derivatives were designed and synthesized by Basu *et al.* as the covalent reversible WZ40028 analogs. Among the synthesized derivatives, 2-cyano-acrylamide scaffolds exhibited strong activity and selectivity against mutants EGFR^{L858R}and EGFR$^{L858R/T790M}$ with IC_{50} less than 2.5 μM. Compound **14** containing polar motif (4-pyridyl group) was found to be the most potent inhibitor with IC_{50} = 37 nM against double mutant EGFR $^{L858R/T790M}$ (Basu, Richters et al. 2015).



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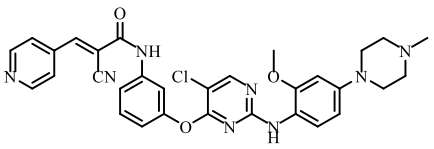

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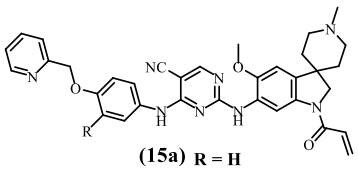
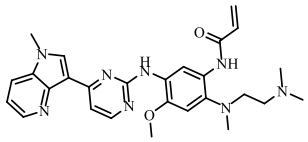
A series of 2,4-diamino-pyrimidine containing spiro structures were prepared and evaluated as dual EGFR and HER2 inhibitors under 0.5 M drug concentration. Compounds **15a,b** showed the highest inhibitory effects against a panel of EGFR kinases especially against both mutants T790M and L858R EGFR kinases which were 31 times more stronger than neratinib as standard drug (IC_{50} ranging from 0.05 to 0.2 μM) (Ye, Zhao et al. 2019).

A new series of 2-aminopyrimidine derivatives were designed based on the structure of osimertinib. Compound **16** showed more selectivity against (EGFR$^{L858R/T790M}$, EGFR^{L858R}) over wild-types EGFR cells (Calu-3 and A431) compared to osimertinib (Zhou, Chen et al. 2018).



(15a) R = H
(15b) R = Cl



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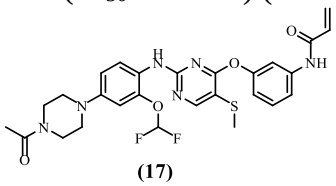
A series of 5-(methylthio)pyrimidine derivatives were synthesized as novel EGFR inhibitors by optimization the structures of WZ4002 and CO168. Compound **17** showed strong enzymatic activity and selectivity against $EGFR^{L858R/T790M}$ over EGFR WT with IC_{50} values of 0.4 nM (Xiao, Qu et al. 2016).

A novel series of 2,4-diarylaminopyrimidine ureas derivatives has been optimized to afford potent and selective inhibitors of the $EGFR^{L858R/T790M}$. The most ideal compound **18** showed high activity against $EGFR^{L858R/T790M}$ kinase (IC_{50} = 4 nM), 22-fold selectivity against wild type EGFR and potent anti-proliferation activity against H1975 cancer cells (IC_{50} = 37 nM) (Zhou, Zhang et al. 2018).



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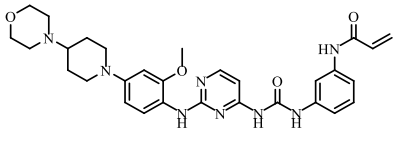

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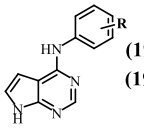
Recent non-covalent mutant $EGFR^{T790M}$ inhibitors

a- Pyrrolopyrimidine-based derivatives

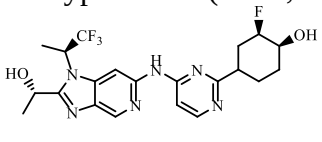
A series of compounds incorporating a pyrrolo[2,3-*d*]pyrimidine scaffold were designed, synthesized and evaluated for dual inhibition of epidermal growth factor receptor kinase (EGFR) and aurora kinase A (AURKA). A number of pyrrolo[2,3-d]pyrimidine-4-amine compounds were evaluated for their inhibitory effects against EGFR. Compounds **19a,b** bearing 3-bromophenyl and 3-bromo-4-chlorophenyl derivatives demonstrated the highest EGFR enzymatic inhibitory with IC_{50} = 3.76 and 3.63 nM, respectively (Kurup, McAllister et al. 2018).



(19a) R = 3-Br
(19b) R = 3-Br, 4-Cl

b- Aminopyrimidine-based compounds

Bryan K Chan *et al.*, described the lead optimization of a noncovalent double mutant (T790M/L858R and T790M/del746-750) selective EGFR inhibitor **20**. The replacement of substituted piperidine by the *N*-alkylsulfonylpyrazole led to one of the most potent compound, **21**, which exhibited improved inhibitory activity against both single and double mutants EGFR ($EGFR^{T790M/L858R}$, $EGFR^{T790M/del\ (746-750)}$, L858R and del746-750), and wild-type EGFR (Chan, Hanan et al. 2016).



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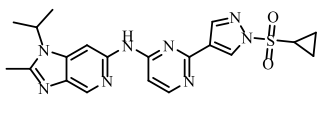

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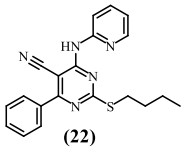
c- 4-Amino-pyrimidine-5-carbonitrile derivatives

A new series of pyrimidine-5-carbonitrile derivatives has been designed as ATP mimicking tyrosine kinase These compounds were synthesized and evaluated for their *in vitro* cytotoxic activities against a HCT-116, HepG2, MCF-7, and A549. Compound **22** showed 4.5- to 8.4-folds of erlotinib activity against HCT-116, HepG-2, MCF-7, and A549 cells with IC_{50} values of 3.37, 3.04, 4.14, and 2.4 µM respectively. In addition, compound **22** was also found to be the most active compound against both $EGFR^{WT}$ and mutant $EGFR^{T790M}$, exhibiting IC_{50} values of 0.09 and 4.03 µM, respectively (Nasser, Eissa et al. 2020).



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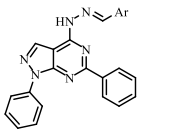
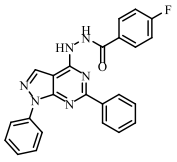
d- Pyrazolo-pyrimidine based compounds

Two series of 1*H*-pyrazolo[3,4-*d*]pyrimidine derivatives were designed, synthesized and evaluated *in vitro* for their inhibitory activities against $EGFR^{WT}$. Compounds **23a,b** and **24** potently inhibited $EGFR^{WT}$ at sub-micro molar IC_{50} values comparable to that of the reference erlotinib. Compound **24** exhibited potent inhibitory activities towards $EGFR^{T790M}$ comparable to osimertinib. Furthermore, compound **24** was a good apoptotic agent, which arrested HepG2 cell cycle at G0/G1 and G2/M phases (Gaber, Bayoumi et al. 2018).



(23a) Ar = 4-NO_2-C_6H_4
(23b) Ar = 1-Naphthyl



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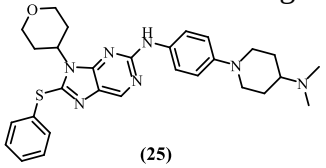
e- **Purine-based derivative**

Several 2,9-disubstituted purine derivatives were evaluated as EGFR inhibitors. Compound **25** displayed the IC_{50} values of 29.4 nM in cell-based assay against HCC827 cell line and 1.9, 104 nM in enzymatic assay against mutant EGFRL858R and $EGFR^{L858R/T790M}$, respectively. This compound significantly inhibited EGFR phosphorylation and remarkably exhibited inhibitory effect in in vivo tumor growth at 5.0 mg/kg by oral administration in mouse HCC827 xenograft model (Hei, Shen et al. 2018).



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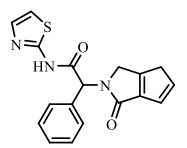
- **The fourth-generation of EGFR inhibitors**

The trials for overcoming EGFR C797S mutation led to the introduction of the fourth-generation EGFR inhibitors to the clinical practice. Thiazole amide derivative EAI001 **26**, is a novel allosteric EGFR inhibitor that bound to the allosteric site near the classic ATP binding pocket, forming the C-helix in the inactive conformation. It exhibited

potent activity against mutant EGFR$^{L858R/T790M}$ and selectivity over wild-type EGFR (EGFR^{WT}) (Engel, Richters et al. 2015). Further optimizations on the phenyl ring led to the introduction of EAI045 **27** (Jia, Yun et al. 2016).



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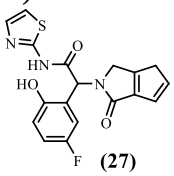

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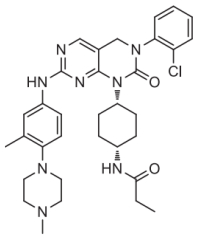
Other fourth-generation of EGFR inhibitors

The urgent need for new small molecules capable of inhibiting EGFR mutations via non-irreversible inhibition of double mutant EGFR$^{T790M/C797S}$ has prompted researchers to find new EGFR allosteric inhibitors [112].

a- Pyrimido-pyrimidinone-based derivatives

A pyrimido-pyrimidinone derivative **28** (JND3229) was identified as a new highly potent selective mutant EGFR^{C797S} inhibitor with single digit nM potency based on random screening among 3000 compounds. Compound **28** potently inhibited enzymatic activity of mutant EGFRC797S (IC_{50} = 5.8 nM), the phosphor- rylation of mutants EGFR$^{L858R/T790M/C797S}$ and EGFR$^{19D/T790M/C797S}$ in BaF3 cells (IC_{50} values of 0.51 and 0.32 µM, respectively). Moreover, this compound demonstrated promising *in vivo* anticancer activity on BaF3 cells xenograft mouse model with EGFR$^{19D/T790M/C797S}$ mutation (Lu, Zhang et al. 2018).



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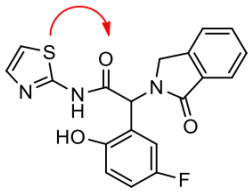
b- **Quinazoline-4-one-based derivatives**

A number of quinazoline-4-one derivatives were designed and synthesized based on the structure modification of the lead compound **29** (EAI045) by the replacement of 2-aminothiazole amide group with non-hydrolysable quinazoline-4-one core. The target compounds were considered as constrained analogues of EAI045 exhibiting improved safety, pharmacokinetic and pharmacodynamic properties. Based on the biochemical assay results, only compound **30** showed EGFR$^{L858R/T790M/C797S}$ inhibitory activity with IC_{50} = 5.3 µM (Lee, Kim et al. 2018).



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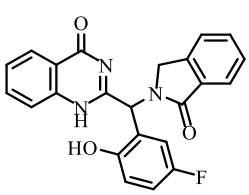

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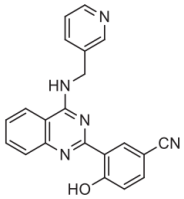
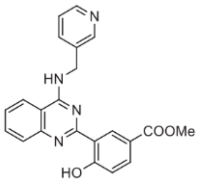
c- Aryl-4-aminoquinazoline-based compounds

New classes of the fourth-generation triple mutant EGFR$^{del746\text{-}750/T790M/C797S}$ inhibitors using 2-aryl-4-aminoquinazoline as the molecular core were discovered based on a two-track virtual screening and de novo design. Compounds **31**, **32**, and **33** reveal more than 1000-fold selectivity for the triple mutant over the wild type, as well as nanomolar inhibitory activity. Strong interactions with the mutated residues (Met790 and Ser797) can thus be invoked to elucidate both the nanomolar inhibitory activity against the triple mutant and high selectivity over the wild type (Park, Jung et al. 2017).



(31)



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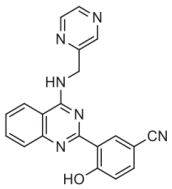
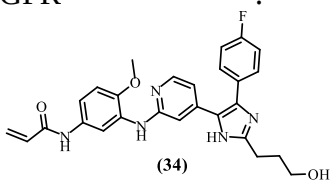


(33)

d- Tri-substituted imidazole derivatives

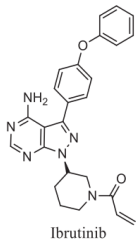
A set of various trisubstituted imidazoles were synthesized and examined the structure-activity relationships (Günther, Lategahn et al. 2017). The attachment of Michael acceptor to the aniline ring led to the most potent compound 3**4** with potent activity against wild and mutant EGFR kinases (EGFR^{WT} and EGFR$^{L858R/T790M}$) and moderate activity against mutant EGFR$^{L858R/T790M/C797S}$.



(34)

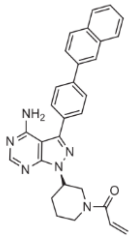
e- Amino pyrazolopyrimidine-based compounds

A set of 4-Amino pyrazolopyrimidine derivatives are introduced as novel mutant EGFR inhibitors based on the structure of ibrutinib **35**. Compound **36** with 2-naphthalene moiety showed promising activity against mutant L858R/T790M/ C797S kinase with IC_{50} of 88 nM (Engel, Becker et al. 2016, Engel, Smith et al. 2017).



Ibrutinib

(35)

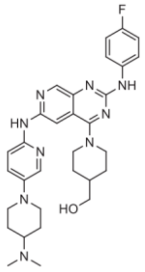


(36)

f- Pyrido[3,4-*d*]pyrimidine-based derivatives

A novel class of pyrido[3,4-*d*]pyrimidine compounds were designed as the new fourth-generation EGFR TKIs. The most promising compound **37** inhibited the

proliferation of HCC827 and H1975 cells with IC_{50} = 0.04 μM and displayed potent inhibitory activities against the mutants $EGFR^{L858R}$ (IC_{50} = 1.1 nM) and $EGFR^{L858R/T790M/C797S}$ (IC_{50} = 7.2 nM) in the enzymatic assays (Zhang, Wang et al. 2018).



(37)

TKI targeting vascular endothelial growth factor receptor (VEGFR)

Vascular endothelial growth factor (VEGF)

Vascular endothelial growth factor (VEGF) is a potent mitogen that is highly specific for vascular endothelial cells. In addition, it is a highly potent angiogenic agent that increases vessel permeability and enhances endothelial cell growth, proliferation, migration, and differentiation (Lee, Jeong et al. 2010).

Vascular endothelial growth factor receptors (VEGFR)

Vascular endothelial growth factor receptor is a tyrosine kinase receptor expressed in endothelial cells. Binding of VEGF to VEGFR induces a conformational change in VEGFR, followed by receptor dimerization and phosphorylation of tyrosine residues (Blum-Jensen and Hunter 2001). The VEGF/VEGFR2 signaling pathway plays an important role in tumor angiogenesis, which stimulates tumor growth by supplying oxygen and nutrients (Li, Gu et al. 2017).

Clinical development of VEGFR-2 inhibitors

Numerous small-molecule VEGF blocking agents have been in the use, and some are in the development pipeline. Besides small molecule inhibitors, some biologics such as ramucirumab (Cyramza®), bevacizumab (Avastin®), ranibizumab (Lucentis®) have been approved to target VEGF and VEGF receptors (Lowe, Araujo et al. 2007, Pavlidis and Pavlidis 2013, Yen, Bai et al. 2018).

Classification of VEGFR-2 inhibitors

VEGFR-2 inhibitors are classified into three types:

A) Type I inhibitors:

Also are known as ATP competitive inhibitors that bind to the region which is accommodated by adenine ring of ATP [82]. Type I inhibitors forms 1-3 hydrogen bonds at the active site of the receptor. Type I inhibitors bind at the hydrophobic-I region by forming a H-bond in the hinge region with Glu917 and Cys919 amino acids. In addition, Asp1046 and Glu885 amino acids present in the linker region can interact by H-bond with the inhibitors. Type I inhibitors do not require the DFG motif to adopt a DFG-out confirmation for binding, and they overlap ATP, so they are considered as the competitive inhibitors. Sunitinib, cediranib, and vandetanib are example of a type I inhibitors.

B) Type II inhibitors

These inhibitors induce inactive activation of DFG-out confirmation of activation loop. These inhibitors are not able to bind at adenine binding site but bind adjacent to the hydrophobic pocket (Liu and Gray 2006). Sorafenib is an example of type II inhibitors.

Type II inhibitors occupy the hydrophobic-II region that is referred as an allosteric site or Phe pocket. With hydrophobic-II region, the selectivity of molecules can be easily achieved (Kornev, Haste et al. 2006). Type II inhibitors, whose scaffolds (hydrophobic I, linker, and hydrophobic-II) only partially overlaps ATP, are indirectly competitive inhibitors (Backes, Zech et al. 2008, Bajorath 2018). In the hinge region, they form a hydrogen bond with Cys919 and Glu917 amino acid residues.

These types of compounds occupy adenine pocket with the specific heterocyclic ring system that can be able to make one to three H-bonds with amino acid residues in the kinase hinge region (Glu917, Cys919). Further, they will also bind to hydrophobic pocket generated by DFG-out conformation (Asp1046-Phe1047-Gly1048) with a specific ring system. A pair of hydrogen bond donor and acceptors (e.g. urea, thiourea, amide, ureido, etc.) is present in the inhibitors which can form the hydrogen bonds with Asp1046 and Glu885 amino acid residues.

Sorafenib, tivozanib, and regorafenib, are example of a type Ii inhibitors (Machado, Peixoto et al. 2015).

C) **Type III inhibitors**

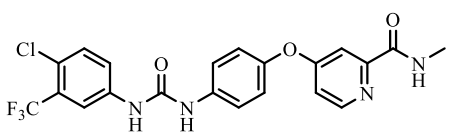
These are covalent inhibitors that covalently bind to cysteine amino acid residue and prevent binding of ATP at the binding site. Vatalanib is an example of type III inhibitors (Kwak, Sordella et al. 2005, Ghorab, Alsaid et al. 2017).

VEGFR inhibitors approved in cancer therapy.

Targeting VEGF receptors represents one approach that has enjoyed a great therapeutic success. Several drugs targeting VEGFRs have been approved for clinical use (Ma, Wang et al. 2016).

a- <u>Biarylurea derivatives:</u>

In 2005,Sorafenib **38** (Nexavar®) is approved for the treatment of advanced renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) (Woo and Heo 2012). Sorafenib, a diaryl urea multiple-targeted antitumor agent, can inhibit several kinases involved in tumor proliferation and angiogenesis including Raf, VEGFR, PDGFR and KIT. In addition, regorafenib **39** (Stivarga®), a fluoro derivative of sorafenib developed by Bayer (Wilhelm, Dumas et al. 2004), inhibits angiogenic kinases VEGFR-1/3. On September 27, 2012, the FDA approved regorafenib **39** for the previously treated metastatic colorectal cancer (mCRC) and then in February 2013, FDA expanded the approved use of regorafenib to treat patients with advanced gastrointestinal stromal tumors (GIST) (DiGiulio 2013).



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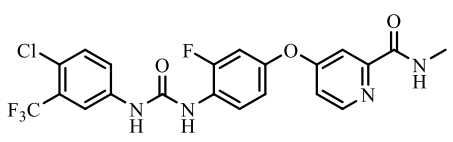
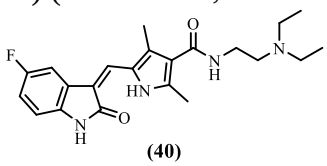


(39)

b- Indol-2-one derivative:

In 2007, Sunitinib **40** (Sutent®) is an oral FDA approved multi-targeted tyrosine kinase inhibitor. It has demonstrated anti-angiogenic and direct antitumor activity against a wide variety of advanced solid tumors. Sunitinib is the standard first-line treatment for metastatic renal-cell carcinoma (RCC) (El Mubarak, Leontari et al. 2018).

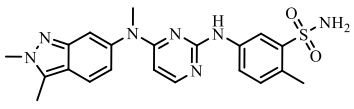


(40)

c- Indazole derivatives:

In 2011,Pazopanib **41** (Votrient®) is aproved by European Medicines Agency (EMA), for the treatment of advanced renal cell carcinoma and advanced soft tissue sarcoma (Herbrink, Groenland et al. 2018). It is a novel multi-targeted receptor tyrosine kinase inhibitor, with both direct anti-proliferative effects and anti-angiogenic properties, targeting the vascular endothelial growth factor receptor (VEGFR-1, -2, and -3), platelet-derived growth factor receptor (PDGFR-a and -b). Pazopanib demonstrates the advantages of broad-spectrum anticancer potency and less prone to resistance (Qi, Chen et al. 2014).

Furthermore, axitinib **42** (Inlyta®), developed by Pfizer as a mutikinase inhibitor. It is a selective inhibitor of vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), which are involved in normal and tumoral angiogenesis (Ho and Jonasch 2011). On January 2012, the U.S. FDA approved axitinib for use in patients with RCC that had failed to respond to a previous treatment.



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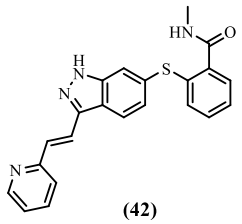
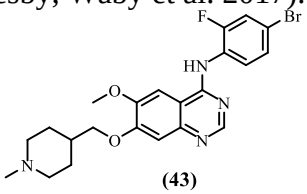


(42)

d- Anilinoquinazoline derivative:

Vandetanib **43** (Caprelsa®), discovered by AstraZeneca, is an orally available tyrosine kinase inhibitor with activity against VEGFR2/EGFR/RET which is currently used in the treatment of medullary thyroid cancer. Vandetanib is representative of a wide class of 4-anilinoquinazoline drug molecules that function as adenosine mimetics and bind at the tyrosine kinase intracellular receptor site.

Other examples of this compound class include Gefitinib **1** (Iressa™) and Erlotinib **2** (Tarceva™) (Brocklesby, Waby et al. 2017).

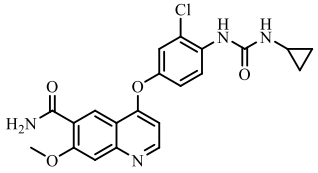


(43)

e- Quinoline derivatives:

Lenvatinib **44** is a potent dual inhibitor of VEGFR-2 (IC_{50} = 4.0 nM) and of VEGFR-3 (IC_{50} = 5.2 nM). On February 13, 2015, the U. S. FDA approved lenvatinib monotherapy is approved for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (Scott 2015). Lenvatinib approved as a combined treatment for advanced renal cell carcinoma following one previous antiangiogenic therapy (Kudo, Finn et al. 2018).

Cabozantinib **45** (Cometriq®) is a multikinase inhibitor that targets VEGFR-2, MET, and RET-TS (Yakes, Chen et al. 2011). Cabozantinib was granted orphan-drug status by the FDA in 2012 for progressive metastatic medullary thyroid neoplasms (Norman 2015).



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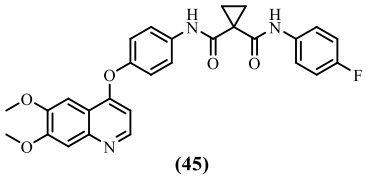


(45)

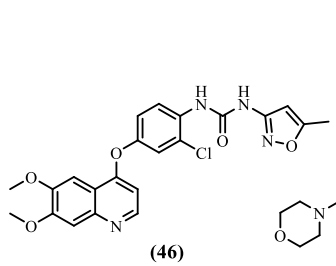
VEGFR inhibitors in clinical trials.

a- Quinoline derivatives:

Tivozanib (AV-951) **46** is a potent inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3, showing IC_{50} values of 0.21, 0.16, and 0.24 nM, respectively (Nakamura, Taguchi et al. 2006).

On the other hand, foretinib (XL880) **47** is a multitargeted inhibitor that is especially active on VEGFR and MET and shows IC_{50} values of 0.8, 6.8, and 2.8 nM against VEGFR-1, VEGFR-2, and VEGFR-3, respectively, and of 0.5 nM on MET (Qian, Engst et al. 2009). Foretinib is being tested in phase I/II clinical trials on solid malignancies as HCC (Huynh, Ong et al. 2012, Shapiro, McCallum et al. 2013).

Moreover, lucitanib (E-3810) **48** is a dual inhibitor of VEGFR and FGFR. It shows IC_{50} values of 7, 25 and 10 nM on VEGFR-1,-2 and -3, respectively, and of 17.5 and 82.5 nM on FGFR-1 and -2, respectively (Bello, Colella et al. 2011).



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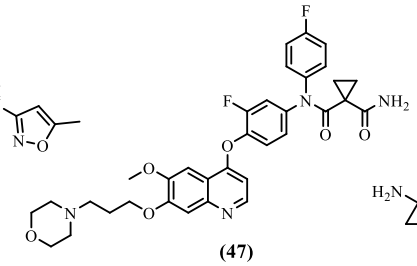

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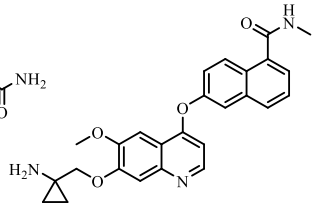
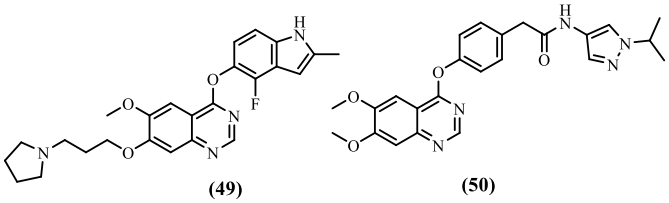


(48)

b- Quinazoline derivatives:

Cediranib (AZD2171) **49** is a potent oral inhibitor of VEGFRs, showing IC_{50} values of 5, 1 and 3 nM toward VEGFR-1, -2 and -3, respectively (Wedge, Kendrew et al. 2005).

AZD-2932 **50** is a potent inhibitor of VEFGR-2 and PDGFRβ with IC_{50} values of 8 and 4 nM, respectively (Plé, Jung et al. 2012).



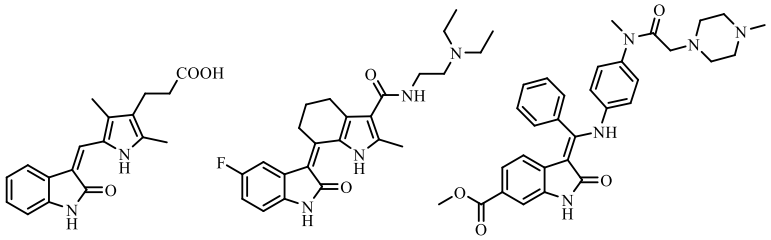
(49) **(50)**

c- Indolinone derivatives:

Orantinib (SU6668) **51**, developed by Sugen, is a soluble and orally bioavailable kinase inhibitor active on VEGFR-2, PDGFRβ, and FGFR-1 with IC_{50} values in the nanomolar range (Sun, Tran et al. 1999). Orantinib is currently being tested in phase I/II clinical trials for the treatment of solid tumors, especially HCC and breast cancer (Kanai, Yoshida et al. 2011, Toi, Saeki et al. 2014).

Tafetinib (SIM010603) **52**, a rigid form of sunitinib, inhibits VEGFR-2, PDGFR, c-Kit, RET, and FLT3 with IC_{50} values in the range from 5 to 68 nM.(Wang, Tang et al. 2012).

Nintedanib **(**BIBF 1120) **53** is a potent, oral angiokinase inhibitor that targets the pro-angiogenic pathways mediated by VEGFR1–3, FGFR, and PDGFR. Nintedanib is currently in phase III clinical trials in non-small cell lung cancer. In addition, it was evaluated against advanced HCC in phase I/II clinical trials (Roth, Heckel et al. 2009, Tai, Shiau et al. 2014).

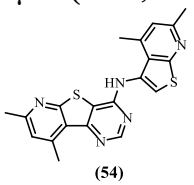


(51) **(52)** **(53)**

The recent development of VEGFR-2 inhibitors

I) ATP competitive type-I VEGFR-2/KDR inhibitors

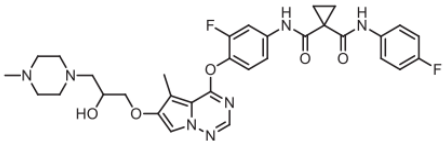
A novel series of tricyclic pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4-amine derivatives were designed and synthesized as inhibitors of KDR. Compound **54** exhibited the most potent and selective inhibitory activity against VEGFR-2/KDR over the six human kinases, with an IC_{50} value 2.6μM (Aziz, Said et al. 2015).



(54)

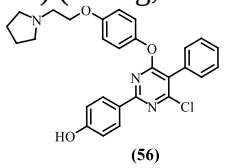
Shi, Wei *et al.* reported pyrrolo[2,1-*f*][1,2,4]triazine derivatives were designed and synthesized as dual VEGFR-2 and c-Met inhibitors. Compound **55** showed potent and selective c-met and VEGFR-2 inhibition with IC_{50} values of 2.3 ± 0.1 nM and 5.0 ± 0.5 nM, respectively. Moreover, the anti-angiogenic activity was also comparable to

reference drug, carbozantinib. Molecular docking results suggest that the compound **55** binds to ATP binding site, and also adjacent to the binding site (Shi, Qiang et al. 2018).



(55)

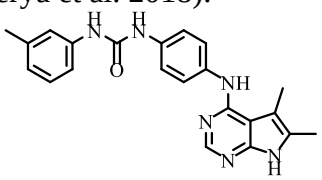
Luo, Guoshun, *et al*. reported 2,4-disubstituted pyrimidines analogs as dual ERα and VEGFR-2 receptors inhibitors for the management of breast cancer. Compound **56**, showed 19 fold increased efficacy as a comparison to tamoxifen in MCF-7 cancer cell line. It and exhibited the best ERα binding affinity (IC_{50} = 1.64 µM) as well as excellent VEGFR-2 inhibition (IC_{50} = 0.085 µM) (Zhang, Liu et al. 2018).



(56)

II) Type-II VEGFR-2/KDR inhibitors

A series of novel pyrrolo[2,3-*d*]pyrimidine based-compounds was designed synthesized and evaluated as VEGFR-2 inhibitors. Compounds **57** and **58** carrying biaryl urea moieties showed potent VEGFR-2 inhibitory activity with the IC_{50} values 11.9 and 13.9 nM, respectively. Furthermore, Compound **57** and **58** exhibited excellent antiproliferative activity towards HUVEC cell line with IC_{50} values 0.31 and 3.74 µM, respectively (Adel, Serya et al. 2018).



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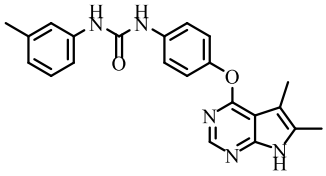
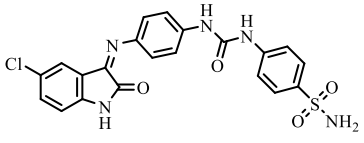


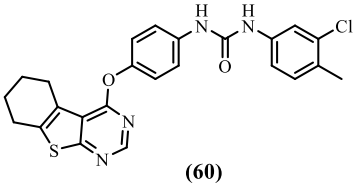
(58)

Eldehna, Wagdy M. *et al*. developed potent and effective indoline urea derivatives as potential anti-hepatocellular carcinoma agents targeting VEGFR-2. Most of the tested compounds exhibited potent inhibition against HepG2 cancer cell line with IC_{50} values in the range of 1.22 ± 0.11 to 8.37 ± 0.85 µM. Compound **59** emerged as the most active counterpart showed potent VEGFR-2 inhibition with IC_{50} value 310 ± 40 µM (Eldehna, Fares et al. 2015).



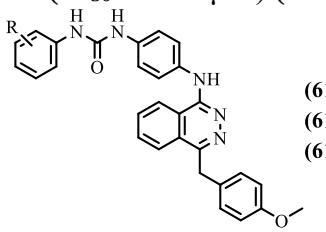
(59)

A series of novel furo[2,3-*d*]pyrimidine and thieno[2,3-*d*]pyrimidine based-derivatives were designed and synthesized as VEGFR-2 inhibitors. The thieno[2,3-*d*]pyrimidine derivative **60**, exhibited a highly potent nanomolar inhibition of VEGFR-2 kinase (IC_{50} = 21 nM).



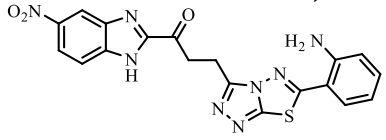
(60)

New 1-substituted-4-(4-methoxybenzyl)phthalazine-based analogs were designed and synthesized as VEGFR-2 inhibitors. The uriedo-anilinophthalazines derivatives **61a-c** showed superior binding affinity (IC_{50} of 0.086, 0.083 and 0.086 µM, respectively) than their anilinophthalazine parents (IC_{50} = 0.083-0.473 µM), which were better than that of the reference drug sorafenib (IC_{50} = 0.09 µM) (Eldehna, Abou-Seri et al. 2016).



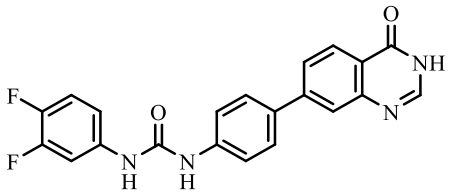
(61a) ; R = 4-CF3
(61b) ; R = 4-OCH_3
(61c) ; R =3-OCH_3

Ibrahim, Heba A. *et al*. reported the design and synthesis of three series of 2-substituted-5-nitrobenzimidazole derivatives hybridized with piperzine, oxadiazole, and triazolothiadiazole moieties as VEGFR-2 and c-Met dual kinase inhibitors. Substitution with phenyl ring connected to oxadiazole ring (compound **62**) showed potent activity on NSCLC (NCI-H522) and melanoma cell line (SKMEL-2) with inhibition of 48.70% and 42.62%, respectively (Ibrahim, Awadallah et al. 2018).



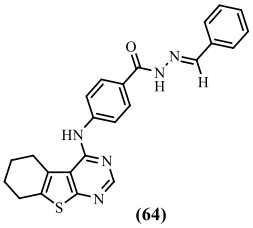
(62)

Zhang L. *et al*. identified a biphenyl-aryl urea derivative bearing a quinazolin-4(3*H*)-one moiety (compound **63**) as potent multi-targeted inhibitor of VEGFR-2, TIE-2, and EphB4 with IC_{50} values 0.77, 8.77 and 3.21 nM respectively (Mainolfi, Karki et al. 2016).



(63)

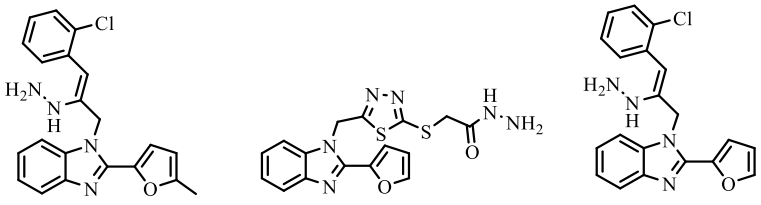
El-Metwally A. Souad *et al*. reported the synthesis of thieno[2,3-*d*]pyrimidines as VEGFR-2 inhibitors. Anticancer activities of the new derivatives were evaluated against three human cancer cell lines (HCT-116, HepG2, and MCF-7) using MTT. Compound **64** exhibited the highest cytotoxic activities against the examined cell lines, HCT-116 and HepG2, with IC_{50} values of 2.80 ± 0.16 and 4.10 ± 0.45 µM, respectively. In addition it showed high activity against VEGFR-2 with an IC_{50} value of 0.23 ± 0.03 µM, that is equal to that of reference, sorafenib (IC_{50} = 0.23 ± 0.04 µM) (El-Metwally, Abou-El-Regal et al. 2021).



(64)

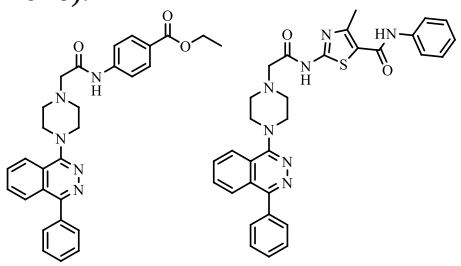
III) Type-III VEGFR-2/KDR inhibitors

Abdullaziz, Mona A. *et al*. discovered a series of benzimidazole-furan hybrids as VEGFR-2 inhibitors. The target compounds were evaluated *in vitro* for their antiproliferative activity against MCF-7 and HepG2 cell lines using SRB assay. Compounds **65** and **66** displayed potent activity towards MCF-7 and HepG2 cell lines. Compound **67** exhibited potent VEGFR-2 inhibition with an IC_{50} value of 0.64 μM (Abdullaziz, Abdel-Mohsen et al. 2017).



(65) (66) (67)

Abou-Seri, Sahar M. *et al*. published the synthesis and evaluation of three different sets of phthalazine analogs based on the 1-piperazinyl-4-phenyl- phthalazine scaffold as effective VEGFR-2 inhibitors. Analogs **68** and **69** exposed potent inhibitory activity against VEGFR-2 with IC_{50} values of 350 ± 30 and 400 ± 40 nM, respectively (Abou-Seri, Eldehna et al. 2016).

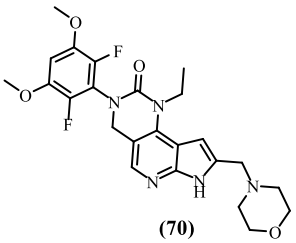


(68) (69)

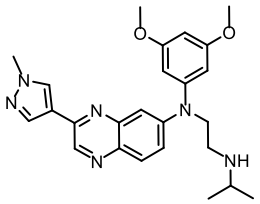
TKI targeting fibroblast growth factor receptor (FGFR)

Fibroblast growth factors (FGFs) facilitate a myriad of physiological functions ranging from early embryogenesis, morphogenesis, and organ formation (Belov and Mohammadi 2013). The FGF/FGFR pathway is also known to play an important role in cellular migration, mitogenesis, and cell death, which implicates its role in oncogenic pathways (Turner and Grose 2010). Pemigatinib **70** and erdafitinib **71** are example of FGFR inhibitors. Erdafitinib is a FGFR inhibitor used to treat locally advanced or metastatic urothelial carcinoma. In early of 2019, the US FDA approved erdafitinib as the first-ever fibroblast growth factor receptor (FGFR) kinase inhibitor indicated for patients with locally advanced or metastatic urothelial carcinoma (Montazeri and Bellmunt 2020). Pemigatinib is a small molecule kinase inhibitor with antitumour activity (Casadei,

Dizman et al. 2019). In April 2020, pemigatinib was approved by the FDA for the treatment of unresectable locally advanced or metastatic cholangiocarcinoma (Hoy 2020).



(70)



(71)

Conclusion

Kinases are crucial mediators of signal transduction processes, and by catalyzing the transfer of phosphates from high-energy donor molecules, such as ATP to other specific substrates, so they are key regulators of a variety of cell functions. One of the largest groups of kinases is protein kinases, which act on and modify the activity of specific proteins. Kinases play a crucial role for kinases in the carcinogenesis and metastases of various types of cancer. However, dysregulation of kinases has been demonstrated in many human disorders including cancer. Therefore, inhibition of PKs has been shown to be a promising therapeutic strategy for treatment of various tumors. We discuss how the challenge of drug resistance to kinase inhibitors is being met and the future of kinase drug discovery.

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التطورات الحديثة في الأدوية التي تستهدف كينازات البروتين لعلاج السرطان

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الملخص:

لا يزال علاج السرطان يمثل تحديًا كبيرًا ويهدد الحياة. في جميع أنحاء العالم ، ثبت أن السرطان هو سبب رئيسي للوفاة بعد أمراض القلب والأوعية الدموية. إن تطوير عقاقير جديدة قادرة على منع تكاثر الخلايا السرطانية بأدنى حد أو بدون أي آثار جانبية على الخلايا السليمة هو مهمة صعبة للغاية. كينازات البروتين عبارة عن إنزيمات موجودة في السيتوبلازم تقوم بفسفرة البروتينات. وهى مسئولة نقل الإشارات في الخلايا حقيقية النواة وتتحكم أيضًا في العديد من العمليات الخلوية الأخرى ، بما في ذلك التمثيل الغذائي والنسخ وتطور دورة الخلية وإعادة ترتيب الهيكل الخلوي وحركة الخلية والتنمية والاستجابة المناعية ووظيفة الجهاز العصبي والاستماتة والتمايز. عادة ، يتم تنظيم نشاط بروتينات كيناز بشكل صارم. ومع ذلك ، في ظل الظروف المرضية ، يمكن أن يؤدي تحرير كينازات البروتين إلى تغيير تعبير كيناز ووظائفه ، وبدء الأورام وبقائها . لذلك ، فإن بروتين كينازات هي فئة مستهدفة جذابة للغاية للتدخلات العلاجية في العديد من الحالات المرضية مثل السرطان. تمثل مثبطات كيناز الآن ربع جميع جهود البحث والتطوير الحالية لاكتشاف الأدوية. لذلك ، يشارك الباحثون في جميع أنحاء العالم في تطوير مثبطات كيناز مستهدفة أكثر كفاءة وأمانًا.

اهداف :

لاستكمال الأدبيات المنشورة حول مثبطات الكيناز السريرية ، قمنا بإعداد مراجعة تلخص مجموعة البيانات الكبيرة هذه في شكل يسهل الوصول إليه لمجتمع الكيمياء الطبية. هنا ، نستعرض التقدم الملحوظ المحرز على مدى السنوات ال 20 الماضية في تحسين فعالية وخصوصية مثبطات الجزيئات الصغيرة من البروتين لعلاج السرطان.

النتائج

باختصار ، فإن إمكانية تطوير أنواع جديدة من مثبطات الكيناز ضخمة ، ونتوقع بثقة أن هذا سيظل مجالا رئيسيا للنمو على مدى السنوات ال 20 المقبلة .

الكلمات المفتاحية: بروتين كينياز , سرطان , EGFR, VEGFR, ABL, BTK , مثبطات الكيناز