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Recent Glimpse Into Quinazoline-based EGFR Kinase Inhibitors for Cancer Therapy

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ABSTRACT

Cancer is one of the prominent causes of mortality globally. Multiple heterocycle-based therapeutic classes are of clinical use for treating cancer. The epidermal growth factor receptor (EGFR) is among one of the vital factors in cancer pathogenesis and progression. To date, three generations of EGFR inhibitors have been approved for cancer treatments. Many heterocycles and their hybrids have been reported as anticancer agents. Among various heterocycles, the quinazoline core has emerged as a promising scaffold for the development of novel EGFR inhibitors (gefitinib, afatinib, erlotinib, and icotinib) due to its higher affinity for the EGFR kinase active site. Additionally, the quinazoline-based molecular hybridization strategy has emerged as an innovative approach to enhance the potency of molecules. This review provides a glimpse into quinazoline derivatives and quinazoline-based EGFR Kinase inhibitors for cancer therapy, along with their structure-activity relationships (SARs).

Keywords: Cancer, EGFR, Quinazoline, Hybrid molecules, SAR.

INTRODUCTION

Cancer still remains a prominent cause for mortality globally, despite various therapeutic advancements for potential anticancer drugs. Vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR) and Human epidermal growth factor 2 (HER2) are among few scaffold present on cell surface. Cell signaling pathways like apoptosis, cell proliferation, angiogenesis and metastasis depends on the EGFR. Heterocyclic ring compounds based on biological activities with pyrimidine, chromone, pyrazole, coumarin, quinoline, pyrazoline, thiazole, and pyridine incorporating sulfur, nitrogen, and oxygen atoms, having remarkable strength to alter their biological and

physicochemical characteristics as anti-neoplastic drugs. Some of the FDA-approved quinazoline-based medicines are shown in Figure 1[1].

EGFR consists of four related transmembrane tyrosine kinase receptor family members that play a crucial role in mediating signaling growth factors in cells by activating numerous vital cellular processes, including cell growth, adhesion, differentiation, division, motility, and death. A less or inactive monomer receptor dimerizes and succeeds in activation via ligand binding to its extracellular site.[2] EGFR/ligand interaction leads to phosphorylation of intracellular tyrosine kinase, initiating downstream signaling resulting in inhibition of apoptosis and cell proliferation (Fig. 2). EGFR overexpression disastrously promotes tumor progression, further encouraging proliferation, leading to non small cell lung cancer (NSCLC), ovarian cancer, colon cancer, breast cancer, head and neck cancer. EGFR consists of an 1186 amino acid polypeptide chain with three active binding areas occupied in the EGFR cavity in the hydrophobic region, an intracellular domain with tyrosine kinase potential, and an extracellular ligand interaction domain[3].

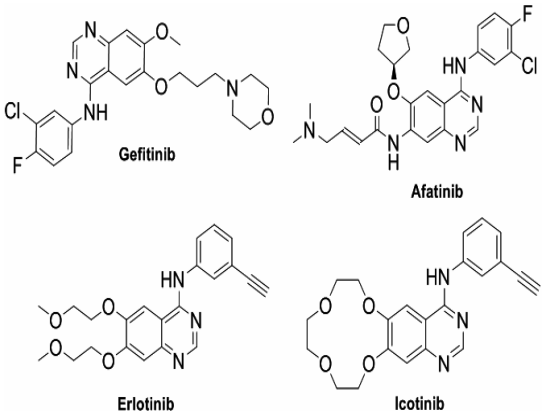


Fig. 1. Clinically approved FDA drugs holding a quinazoline scaffold as EGFR inhibitors[3]

The outline of this review focuses on synthesized potential EGFR inhibitors and exploration of impactful key modulations of the pyrazole core as anticancer effect, intended as a guide for future rational design, synthesis, and generation of pyrazole-based EGFR inhibitors[4]. Via performing a Scopus-based database search on pyrazole, we analyzed enhanced interest in respective years. Based on extensive data on pyrazole-based EGFR inhibitors, we aim to elucidate SAR principles, with synthesis methods to be discussed in future work[5].

Datasets

One of the key components of any *in silico* approach is the development of standard datasets for model testing, training, and validation. In this work, we develop three distinct models to predict inhibitors against both mutant and wild-type forms of EGFR. As a result, we produced three different kinds of database for every type of models, as explained further[6].

Datasets for wild-type EGFR

Data gathered experimentally verified 128 antiEGFR quinazoline derivatives or quinazoline based EGFRi from literature survey to create various model against the wild type of EGFR. These inhibitors were referred to as wild type inhibitors in this work, and the dataset that includes all 128 inhibitors is known as the wild whole database. We randomly split our dataset into two sets: a validation set (20% inhibitors) and a training set (80% inhibitors) to give an objective assessment of our models. In conclusion, we generated three datasets, each containing 128, 103, and 25 inhibitors, respectively: wild valid, wild train, and wild whole.

Mutant type EGFR

We acquired 56 imidazothiazole and pyrazolopyrimidine-based inhibitors against the mutant EGFRL858R, along with their IC_{50} values from the literature. Additionally, inhibitors have been identified against the wild-type of EGFR. The dataset containing these 56 anti-EGFR mutant inhibitors was created from the whole mutant dataset, and they were referred to as mutant-type inhibitors. Like the wild datasets mentioned above, we generated three datasets, entitled mutant valid, mutant whole, and mutant train, each of which contained 56, 42 (80%), and 14 (20%) inhibitors, respectively.

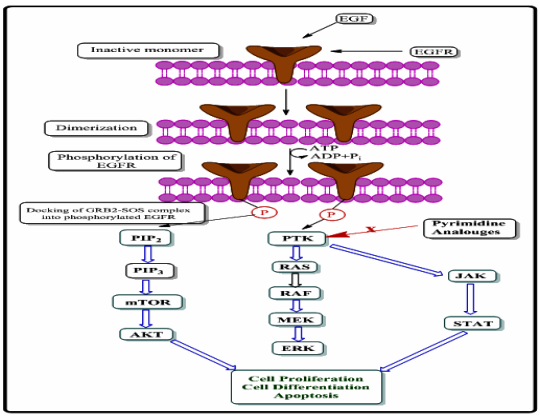


Fig. 2. Mechanism illustrating the signaling pathway responsible for EGFR[6]

Hybrid datasets

A hybrid or combined dataset was developed with 128 wild + 56 mutants (184 inhibitors) to predict models for EGFR inhibitors against both mutants and wild EGFR. Additionally, this dataset was separated into 3 database: hybrid whole, valid, and hybrid train, each containing 184, 37, and 147 inhibitors, respectively.

EGFR family

Since its discovery, EGFR has been recognized as a biomolecular target for cancer treatment. The transmembrane glycoprotein EGFR has a molecular weight of 170 kDa and an N-terminal glycosylation site. Although the EGFR gene is active in various cancers, brain and head and neck tumors exhibit particularly high levels of it. The EGFR family is the researcher's primary focus for improving cancer treatment. Table 1 Lists the synonyms and the identification of the four EGFR family members: EGFR, ErbB2, ErbB3, and ErbB4[8].

Table 1: Discovery and synonyms of four different members of the EGFR family[9]

Sr. No	Receptor	Synonym	Discovery
1	EGFR	erbB1, HER	Ullrich *et al.,* (1984) and Carpenter *et al.,* (1975)
2	ErbB2	HER2, neu	Bargmann and Weinberg (1988); Stern *et al.,* (1986)
3	ErbB3	HER3	Plowman *et al.,* (1990)
4	ErbB4	HER4	Plownman *et al.,* (1993)

Role of heterocyclic compounds as EGFR inhibitors

Heterocycles have been widely explored and utilized for evaluating their biological activity against various classes of cancer, including colon, ovarian, and lung cancer. This review enables the consideration of various fused pyrimidine derivatives with potential activity as EGFR kinase inhibitors. Pyrimidine fused with heterocycles such as thiophene, pyridine, piperidine, pyrrole, pyran, acridine, and with phenyl rings could help obtain potency as anti-cancer agents[10].

First generation of EGFR inhibitors

Most of the 1st generation EGFR inhibitor holds a pyrimidine core for the treatment of NSCLC, such as gefitinib (in 2003), erlotinib (in 2004), as 1st line therapy for locally complicated, advanced, or pancreatic cancer (in combination with gemcitabine), and icotinib (Fig. 3). Whereas the Phase III clinical trial illustrates an enhanced period of free survival (PFS) for gefitinib when compared with paclitaxel or carboplatin as 1st line therapy in the EGFR-positive mutation group, an improved health related quality index of life, a higher objective response rate, but no improvement in overall survival[11]. The main drawback of 1st-generation drug inhibitors is the development of secondary mutations after a median period of 12 months. *In vitro* studies show a 50-fold lower affinity of gefitinib compared to EGFRG719S compared to EGFRL858R, with a 14-fold increase in affinity towards ATP compared to EGFRwt.

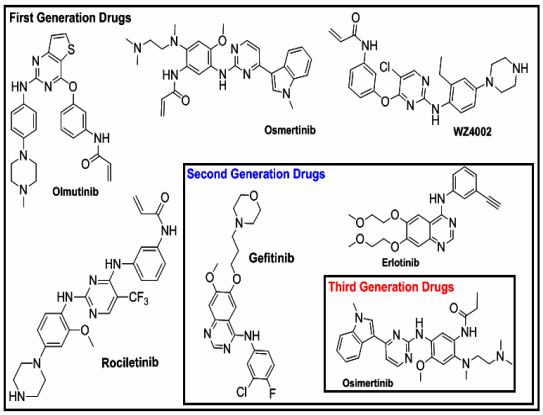


Fig. 3. Incorporates all generations of EGFR drugs[11]

Second generation of EGFR drugs

The acquired resistance to 1st generation EGFR is prompting the evolution of second-generation EGFR TK inhibitors (TKIs). Development of second-generation TKIs was to overcome resistance acquired against first-generation drugs, with the potential to be more efficient than gefitinib or erlotinib as the first EGFR inhibitors (Fig. 3). It is observed that the 2nd generation forms an irreversible, covalent interaction with the EGFR kinase region and may exhibit additional activity against various similar receptors/structures within the EGFR family, such as VEGF. In addition, due to covalent binding, this class of drugs tends to exhibit higher activity against EGFRT790M or other secondary mutations, whereas 1st-generation medications appear to be ineffective[12].

Table 2: EGFR TKIs and their various receptor targets[13]

Drug	EGFR	ERBB4	HER2	VEGFR	Reversible	Other
Gefitinib	x				x	
Afatinib	x		x			
Dacomitinib	x	x	x			
Vandetanib	x			x	x	RET
Erlotinib	x					

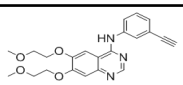
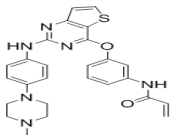
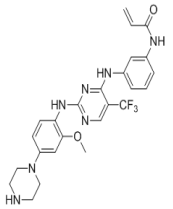
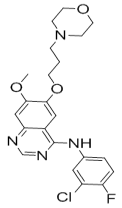
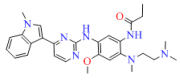
Third generation of EGFR inhibitors

Osimertinib is one of the only approved drugs for TK inhibition (Fig. 3). Given the limited efficacy of FDA-approved drugs such as afatinib, which circumvent EGFRT790M resistance, the first and second generations of EGFR TKI's have led to the generation of the 3rd Gen of EGFR TKI's (refer to Fig. 2). This class includes olmutinib, rociletinib, osimertinib, and avitinib. The defining characteristic of belonging to the class has a significantly greater affinity in EGFR mutant cells than in EGFRwt cells, making them more mutant-selective[14].

FDA approved inhibitors

Various approved drugs, such as erlotinib and gefitinib, are already on the market. It exhibits a broad spectrum of biological activity, including antimicrobial, analgesic, anticancer, and antioxidant properties. Table 3. Depicts names of some clinically approved pyrimidine-based drugs with therapeutic agents as anticancer drugs.

Table 3: Indicating a few FDA-approved drugs to treat various cancers[15]

Sr. No	Drug	Structure	Clinical Indication
1	Erlotinib		Currently approved for metastatic NSCLC
2	Olmutinib		EGFR-TK inhibitors
3	Rociletinib		EGFR-TK inhibitors
4	Gefitinib		Approved to treat advanced/metastatic NSCLC
5	Osimertinib		Clinical efficacy against NSCLC

Quinazoline-based derivatives as EGFR inhibitors

Quinazoline and pyrimidine-based compounds are the two primary types of EGFR inhibitors. It is established that NSCLC occurs due to mutations in the EGFR tyrosine-kinase domain. L858R, which makes up around 41% of all activated mutation, is one of the most prevalent oncogenic mutations. By interfering with auto-inhibitory connections, this EGFR mutation activates the kinase, resulting in ligand-independent stimulation of TK activity, which in turn promotes cancer[16].

Quinazoline-pyrimidine-based moiety derivatives

As innovative antiproliferative drugs, a novel class of quinazoline fused pyrimidine hybrid compounds, 6a-6n, have been developed and synthesized. Biological activities of these compounds hold antiproliferative properties, assessed using 3 human cancer cell lines (SW-480, A549, and MCF-7). IC_{50} values against the above-mentioned cell lines, ranging from 2.3 ± 5.91 to 176.5 ± 0.7 µM, were recorded; the synthesized molecules showed acceptable potential. In addition, IC_{50} values of 5.65 ± 2.33 µM, 5.9 ± 1.69 µM and 2.3 ± 5.91 µM against MCF-7, A549 and SW-480 were recorded, compound 6n exhibited the strongest antiproliferative activity (Fig. 4). Results showed that 6n might cause the A549 cell line to undergo dose-dependent apoptosis and stop in the S phase of the cell cycle[17].

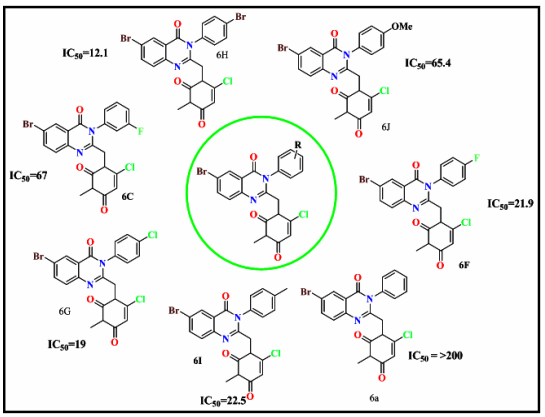


Fig. 4. Antiproliferative activities of compound 6a-6n against the MCF-7 cell line[17]

Quinazolin-4(3h)-one based substitutions

For inhibiting EGFR, 19 novel quinazolin-4 (3H)-one analogs, 6a-l and 3a–g (Fig. 5), were developed and synthesized. The anti-proliferative properties of the produced derivatives were investigated *in vitro* against sixty distinct human cell-lines. With $GI_{50} = 0.789$ µM, the highest effective compound, 6d, demonstrated better submicromolar antiproliferative activity against the NCI-H460 NSCLC cell line. Strong cytostatic action against 40 distinct cancer cell lines was also observed by it (TGI range: 2.590–9.550 µM). With an IC_{50}

value of 0.069 ± 0.004 µM, molecule 6d effectively repressed EGFR, whereas erlotinib had an IC_{50} value of 0.045 ± 0.003 µM (Fig. 4). Compound 6d produced cell cycle arrest at the G1/S-Phase in the breast cancer cell line HS-578T and demonstrated a 16-fold enhancement in overall apoptosis[18].

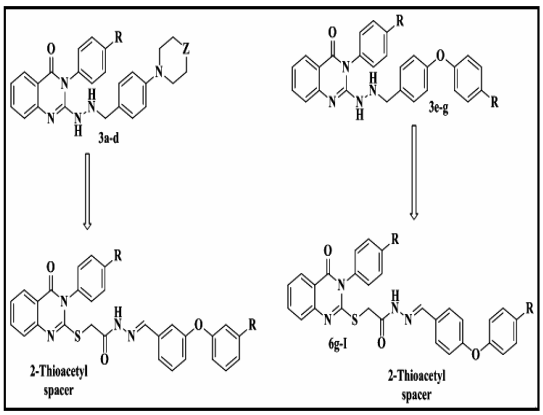


Fig. 5. Targeted designed compounds against EGFR[18]

Quinazoline-based thiazole EGFR tyrosine inhibitors

A novel class of thiazole compounds based on quinazolines was investigated for its potential anticancer effects. Synthesized quinazoline fused thiazole molecules (4a-j) were employed against 3 cancer cell-lines, MCF-7, A548, and HepG2, in addition to the Vero cell lines. Each of these substances exhibited a regular to considerable cytotoxic effect, which was apparent and, in a few cases, far more intense than that of the commonly prescribed medication, erlotinib. Compound 4i IC_{50} values for the A549, MCF-7, and HepG2 cell lines were 14.79, 2.86, and 5.91 µM, respectively, whereas compound 4j was 3.09, 6.87, and 17.92 µM (Table 4). All the synthesized derivatives were examined for their *in vitro* inhibitory activities against several EGFR kinases, including the wild-type, EGFRL858R/T790M, and EGFRL858R/T790 EGFRM/C797S. Compound 4f had IC_{50} values of 3.62, 2.17, and 2.81 nM against the wild-type, EGFRL858R/T790 EGFRM/C797S, and EGFRL858R/T790 M mutant EGFR-kinases, respectively[19].

Table 4: Cytotoxicity of synthesized derivatives 4a-4j on various cancer cell-lines[19]

Compound	IC_{50} (µM) MCF-7	HepG2	A549	Vero
4a	6.210±0.330	11.860±0.710	24.730±0.950	>50
4f	3.710±0.470	7.920±0.630	19.020±0.830	>50
4g	4.140±0.690	9.360±1.150	20.840±1.240	>50
4i	2.860±0.310	5.910±0.450	14.790±0.950	>50
4j	3.09±0.220	6.870±0.510	17.92±0.950	>50

Novel synthesized quinazoline-based analogs as dual inhibitors (EGFR/HER2)

The resistance to EGFR resulting from the overexpression of HER2 is typically believed to be addressed by EGFR/HER2 dual-target inhibitors. This research examines the structure based synthesis and in vitro assessment of quinazoline substituents as dual target EGFRi and HER2i. II-1 demonstrated (Fig. 6) intriguing antiproliferative activity against PC-9/NCI-H358/NCI-H1781/Calu-3, while II-2, III-3, and III-4 demonstrated similar inhibition activity against HER2 and EGFR (EGFR IC_{50} = 0.30 nM, HER2 IC_{50} = 6.07 nM, NCI-H358 GI_{50} = 23.30 nM, PC-9 GI_{50} = 1.95 nM, Calu-3 GI_{50} = 23.13 nM, NCI-H1781 GI_{50} = 41.61 nM)[20].

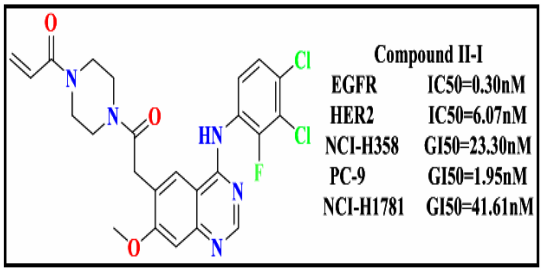


Fig. 6. Activity of lead compound among synthesized derivatives against several cell lines[20]

N-(3-(3-phenylureido) quinoxalin-6yl) acrylamide derivatives

N-(3-(3-phenylureido)quinoxalin-6-yl) acrylamide substitutes (7a-m) are designed, synthesized, docked, and evaluated in vitro against EGFR mutant forms. In the nanomolar range, compounds seven h and 7I exhibited biochemical activity against EGFRL858R and EGFRwt. Calculations of reaction enthalpy and molecular docking have demonstrated how the combination of covalent and reversible interaction mechanisms with EGFR affects the inhibition effect. In a list of selected thirty cell-lines derived from bladder, prostate, breast, melanoma, colon pancreatic, and ovarian malignancies, the inhibitory profile of 7 h was established (Fig. 7), showing specific growth inhibition of EGFR-associated cells at 10.0 µM. Identifying small compounds that can block clinically relevant EGFR-mutant forms is crucial, and new chemical motifs may provide insights into EGFR form selectivity, offering novel approaches to overcoming existing therapeutic limitations[21].

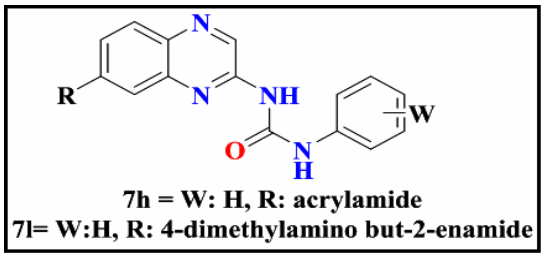


Fig. 7. Molecular concept for quinazoline derivatives designed as EGFR inhibitors[21]

Sar of quinazoline-based derivatives against egfr

The author designed and synthesized various quinazoline-based derivatives against the EGFR kinase. A series of compounds were synthesized, and among them, 45a was found to be actively potent against EGFR with an IC_{50} of 0.13 µM, whereas for VEGFR, it was found to be 0.56 µM (Fig. 8). Antiproliferative activity was also assessed, yielding an IC_{50} of 31.23 µM against HT-29, whereas for MCF-7, it was recorded to be 39.02 µM[22].

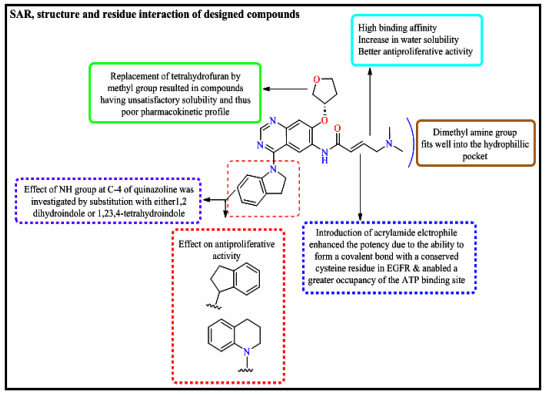


Fig. 8. SAR, Structure of (R,E)-4-(dimethylamino)-N-(4-(indolin-1-yl) quinazoline[22]

Pyrimidine-based derivatives

Pyrimidine belongs to intriguing heterocyclic compounds with a vast range of biological activities, and it has also gathered real attention, especially from the anticancer society, and numerous patents have been filed bearing the pyrimidine scaffold (Table 5). A multitude of pyrimidine moiety-based analogues were designed, synthesized, and their in-vivo activity evaluated for efficacy in targeting several protein kinase enzymes, including the EGFR tyrosine kinase[23]. These scaffold compounds were designed for targeting mutations in the TK region of EGFR and for effective treatment against various cancers such as NSCLC. Osimeritinib was the first pyrimidine-based anti-cancer drugs approved by the FDA, belonging to the third-generation class of EGFR kinase inhibitors. Olmutinib and rociletinib were also designed based on the hypothesis derived from osimeritinib[24].

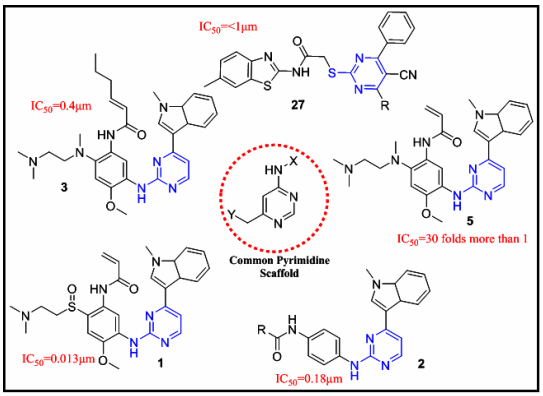


Fig. 9. Structures of 2-amino pyrimidine-based derivatives against EGFR TKIs[24]

To show cancerous and antiproliferation cell inhibition via the synthesis of pyrimidine-based quinazoline substitues. Further, in vitro cytotoxicity was investigated against 3 active human cell-lines: MCF, SW1116, and A549, depicting values as much less than 10-12µM via utilizing colorimetric MTT assay, cisplatin as a reference drug. Compounds H3, H5 and H6 showed IC_{50} as 5.75.7±0.6, 5.4±0.6 and 9.35±1.15 µM when compared with cisplastin to 12±1.9 µM. Cytotoxicity studies on SW1116, apart from the H4 and H11 compounds, all showed higher IC_{50} values compared to cisplatin. In contrast, with MCF-7, only H3, H4, and H11 showed lower IC_{50} values compared to cisplatin[25].

Table 5: Patents on pyrimidine scaffold-synthesized molecules as EGFR[26]

Sr. No	Patent Number	Patent date	Inventors	Descriptors
1	EP3400216A4	14-Aug-2019	Peter Dove and Abdelmalik Slassi	Newly designed fluorinated quinazoline substitutes as EGFRi
2	EP3567030A1	13-Nov-2019	Lihong Hu, Xile LIU, Haiwen Wan, Charles Z. Ding, Lingyun Wu, Shuhui Chen	Quinazoline compound for EGFR inhibition
3	CA2942887C	20-Aug-2019	Ulrich Bierbach, Amanda J. Pickard, Mu Yang	Tyrosine kinase inhibitors comprising gold and platinum quinazoline derivatives
4	EP3246328A1	22-Nov-2017	Wang Sheng, Zhiyong Pan, Leifu Yang	Quinazoline based heterocyclic derivative as an EGFR kinase inhibitor, application and preparation there of
5	US984049482	12 Dec,2017	Heshen Zhang, Yingwei Chen, Guanguai Zeng	Quinazoline derivatives

2,4,5,6-tetrasubstituted pyrimidines

According to a reported study, the effects of ER-alpha and VEGFR-2 molecules in the active state of 2,4-disubstituted pyrimidine analogs were analyzed against MCF-7 cell lines. Compound 20 depicted binding affinity against ER-alpha with an IC_{50} of 1.64 µM and inhibiting VEGFR-2 (IC_{50} = 0.085 µM) (as shown in Fig. 10). It acts by lowering progesterone levels through the inhibition of *in vivo* angiogenesis, as well as mRNA. Suppressing apoptosis, cell migration, and transduction resistance of ERK/MAPK/Raf-1 were observed in the MCF-7 cell line. In addition, another series includes iminopyrimidine, arylidine derivatives of thiazolopyrimidine, thioxopyrimidine, and bicyclic thiazolopyrimidine, which have been reported in anticancer studies against PC-3, HCT-116, and Hep 2 cancer cell lines. Molecules 21a, 21b, and 21d were found to be the most potent against PC-3[27].

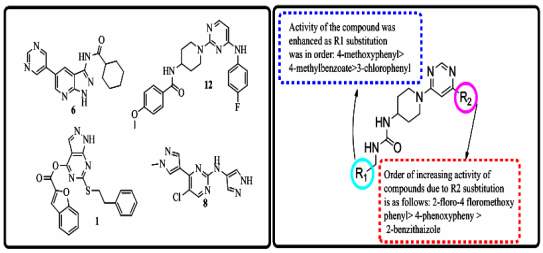


Fig. 10. SAR and structures of the most active synthesized compounds[27]

Pyrazole-thiadiazole-based derivatives

The activities of synthesized molecules were elucidated through an MTT assay (for toxicity studies) against the A549 cell line, alongside analysis of mitochondrial membrane potential using flow cytometry with EGFR inhibition. As a result, compound 6d, 6g and 6j illustrated highest IC_{50} against selected A549 cells (6d; IC_{50} = 5.176±0.164; 6g; IC_{50} = 1.537±0.097, 6j; IC_{50} = 8.3493±0.667 µM) respectively (Fig. 11). Concluding MMP flow cytometry, 6 g depicted 80.93%, whereas 6 g showed inhibition against EGFR kinase with an IC_{50} of 0.024±0.002 Mm.

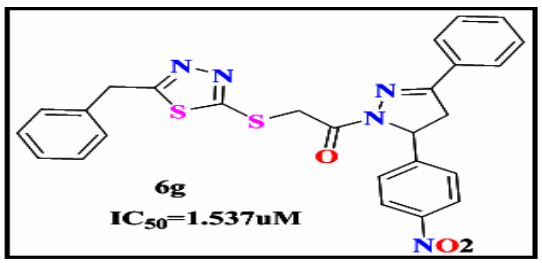


Fig. 11. EGFR inhibition activity against the MCF-7 cell line[28]

Pyrazolo[1-5-a]pyrimidine analogs

The pyrazolo[1,5-a]pyrimidine core on the heterocyclic center affects biological activity and is a useful motif for creating drug-like compounds. Pyrazolopyrimidine substituents 6a-o were designed and developed to provide safer and more effective anticancer drugs. Several spectroscopic methods and elemental analysis verified the purity and structure of the resultant molecules. The anticancer activities of the synthetic compounds have been tested on human cancer cell lines, such as HCT116 (colorectal), HepG2 (liver), and MCF-7 (breast). Most pyrazolopyrimidine derivatives showed cytotoxic effects; however, only a few are significantly more effective than sorafenib and doxorubicin. For MCF7, HepG2, and HCT116, the compound 6b IC_{50} values were 3.19, 3.26, and 5.01 µM, respectively[29].

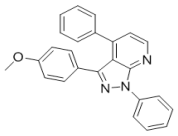
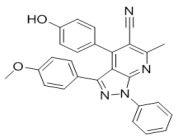
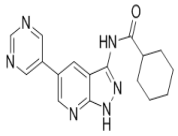
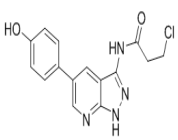
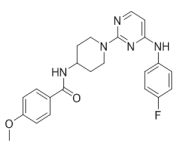
The most potent compounds were investigated for cytotoxicity (MTT) against the WI-38 cell-line, a typical, healthy cell-line, to calculate their selectivity. To ascertain their mode of cytotoxicity, inhibition experiments for HER2 and EGFR were also conducted. The most efficient dual HER2/EGFR TKIs were compound 6a, which had IC_{50} values of 0.116 (HER2), 0.163 (EGFR), and compound 6b, which had IC_{50} values of 0.083 (HER2), 0.126 (EGFR). Lastly, molecular docking studies demonstrated that compounds 6a and 6b exhibit a strong hydrogen bonding interaction with EGFR and HER2, resulting in the irreversible dual inhibition of these kinases. The compounds demonstrated promising therapeutic properties and could serve as models for future development[30].

Pyrazole-fused pyrimidine derivatives

Synthesis of pyrazolo based pyridines and to evaluate their anti-cancer effect against MCF-7, HCT116, and HeLa cell lines. Results show the most potent activity against HeLa among all the substitutes, compared to doxorubicin (the reference drug). Molecule 5 exhibited viability toxicity in both HCT116 and MCF-7 cell lines, inducing apoptosis andcell-cycle arrest against tested cell-lines. In contrast, compound 4 induced S-phase arrest in the HCT116 cell line. Furthermore, compounds 4 and 5 showed potent inhibition against CDK9 and CDK2. In other work, compounds 6 and 7 showed inhibition at 10µm concentration against CDK2/ cyclin A (96% inhibition)[31].

The author designed novel fused compounds of pyrimidine-pyrazole amine as EGFR inhibitors targeting specifically CDK2 (Table 6). Among the analyzed substitutes in the mentioned table, the highest activity is observed against several selected human cell lines, arresting the cell cycle in the G2/M and S-Phases, which leads to apoptosis. A designed piperidine-pyrimidine substitute against CDK2, compound 12, is found to be a potentially active inhibitor, demonstrating a vast range of anticancer agents against selective human (breast cancer) cell lines, such as MB-468. Furthermore, the investigation shows that the addition of a 4-OCH_3 group at phenyl amid position plays a crucial role as an anticancer agent. Substitution of 4-fluoro conferred the highest inhibition, while replacement of R with 4/2-methyl leads to a lower activity. These compounds are key factors for significant interactions in the ATP binding sites of CDK2, incorporating H-bond with LEU83 and an anion interactions with ASP86. These vital interactions play a crucial role in binding affinity against CDK2, emphasizing its therapeutic efficiency for breast cancer[32].

Table 6: Holds the data of IC_{50} against various cell lines of synthesized compounds[31,32]

Compound	Structure	Examined cancer cell lines		CDK2
		Cell lines	IC_{50}/IG_{50}	IC_{50}
4		Hela	2.59 µM	1.63 µM
5		MCF-7 4.66 µM	HCT116 0.46 µM	1.98 µM
6		-	-	0.36 µM
7		-	-	0.66 µM
12		NA	NA	54.4 nM

CONCLUSION

Highest incidence of most common cancers worldwide is lung cancer. Finding EGFR receptor inhibitors to treat lung cancer, particularly (NSCLC or EGFR tyrosine kinase mutations, was one of the main issues addressed by medicinal chemists. Because the mutation causes treatment resistance, treating EGFR tyrosine kinase to control NSCLCs has become an essential therapeutic necessity. Several TKIs with significant therapeutic usefulness in a variety of cancer types (particularly NSCLC) were developed because of the discovery that the quinazoline core is a useful scaffold for EGFR inhibition. Many research groups have long been interested in identifying the essential structural characteristics of an optimal EGFR TKI, which include little off-target effect, minimal affinity for EGFRwt, and improved potency toward mutant versions of EGFR. Based on newly synthesized quinazoline derivatives over the past six years, this work offers a set of general drug design guidelines for the creation of new quinazoline based derivatives as possible EGFR-inhibitors. The involvement of substituents and the position at the quinazoline moiety are two components of the varied biological actions of quinazoline-based medications that provide insight into the relationship between the drug and the target. As a result, thorough and critical investigation of quinazoline's different substituents is essential for possible medication development. Design and synthesis of medications based on quinazoline scaffolds for more safer treatment of numerous fetal disorders in the future will greatly benefit from this review.

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Conflict of interest

The author declare that we have no conflict of interest.

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Author Contribution

Conceptualization, M.I., F.N.A., and T.S.A.;

methodology, B.A.A and Y.H.A.; analyses, M.I. and Y.H.A; writing-original draft preparation, N.S.A. and U.I.D.; writing, review and editing, M.I.S; supervision. All authors have read and agreed to the published version of the manuscript.

Data Availability

All data supporting of this study are contained within the article.

Ethical Approval

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

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