DOI: 10.12923/cipms-2025-0018 Curr. Issues Pharm. Med. Sci., Vol. 38, No. 2, Pages 112-121

Current Issues in Pharmacy and Medical Sciences
Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

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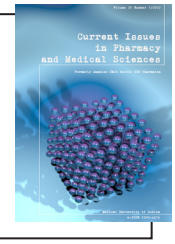

Recent development of heterocyclic scaffolds as EGFR kinase inhibitors in cancer

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ARTICLE INFO

Received 03 May 2024
Accepted 11 August 2024

Keywords:
cancer,
heterocyclic scaffolds,
kinase inhibitors.

ABSTRACT

The Epidermal Growth Factor Receptor (EGFR) is responsible for cell differentiation and proliferation upon activation when it binds to one of its ligands. It is thought to be involved tumorigenesis, which is implicated in cancers such as lung cancer and breast cancer. Over the past decades, the EGFR has become extensively examined as a target for the development of new anticancer agents. Several EGFR tyrosine kinase inhibitors (TKIs) have been identified and assessed in clinical trials as potential treatments for carcinoma. This review provides updated information on Novel heterocyclic scaffolds, which are now considered important pharmacophores that have demonstrated significant potency as EGFR inhibitors. Kinase inhibitors, in the last few years, have emerged as emerging anticancer agents with promising results. In this review, we briefly discussed heterocyclic scaffolds and the structural activity relationships of lead compounds such as substituted quinazoline, pyrimidine, quinoline and indole as EGFR kinase inhibitors, as well as their use as anticancer agents. Information on miscellaneous heterocyclics such as thiazolyl-pyrazoline derivatives, pyrazole derivatives and oxadiazole derivatives is also included.

INTRODUCTION

As per the estimate published by specialised cancer agency of the World Health Organisation, Global cancer observatory (GCO), Cancer is the second leading cause of death globally and there were approximately 18.1 million new cancer cases worldwide and about 9.6 million cancer-related deaths and this burden is expected to grow to 27.5 million new cancer cases and 16.3 million cancer deaths worldwide due to the aging and population growth [1]. Findings based on research study suggest that mitogen activated protein kinase (MAPK) signalling pathway have crucial role in cancer. Kinase enzyme plays intrinsic role in cell initiation, survival and proliferation. Tyrosine kinase is one of the critical conveyers of signal transduction and mutation. Tyrosine kinase is responsible to controls fundamental cellular mechanism such as growth, proliferation, differentiation, migration and apoptosis. It is also reported that inhibition of catalytic phosphorylation of tyrosine leads to inactivation of dimer that further inactivates signalling pathway for proliferation of disease such as cancer [2].

The inhibition of epidermal growth factor receptor (EGFR) plays crucial role in tumour expression, angiogenesis and metastasis. The receptor tyrosine kinase family known as the epidermal growth factor (EGFR) consists of four subtypes of receptors EGFR (erb 1), HER2 (erb2), HER3 (erb3) and HER4 (erb4) [3]. Ligands (EGF, TNF) bind to ligand binding site (EGFR) leading to dimerization and catalytic phosphorylation (transfer one phosphate to other). After phosphorylation signalling pathway of EGFR regulated by GTPase enzyme which control in "on" or "off" way which is responsible for the proliferation, oncogenesis, survival and migration of cell in nucleus and this continuous activation of signalling pathway leads to cell division in cancer. [4].

As per the literature different heterocyclic scaffolds are having EGFR inhibitory activities. EGFR inhibitors are acting by competing at the catalytic site for binding with ATP. The number of compounds bearing heterocyclic scaffolds molecules designed and synthesized that inhibiting catalytic activity of EGFR tyrosine kinase.

Quinazoline scaffolds as EGFR kinase inhibitors

Quinazoline has proven to be highly effective in treating cancer and has been used as most important heterocyclic moiety in new drug discovery. Most lead compounds synthesized based on quinazoline moiety and tested for its diverse biological activities also [5]. The emergence of EGFR mutations as a significant hurdle in the quest of innovative

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inhibitors of EGFR has prompted the development of successive generations of Quinazoline compounds (Figure 1). These are known as EGFRIs [6]. The investigation of EGFR inhibitors like erlotinib and lapatinib has highlighted the crucial contribution of quinazoline moiety in their anticancer properties.

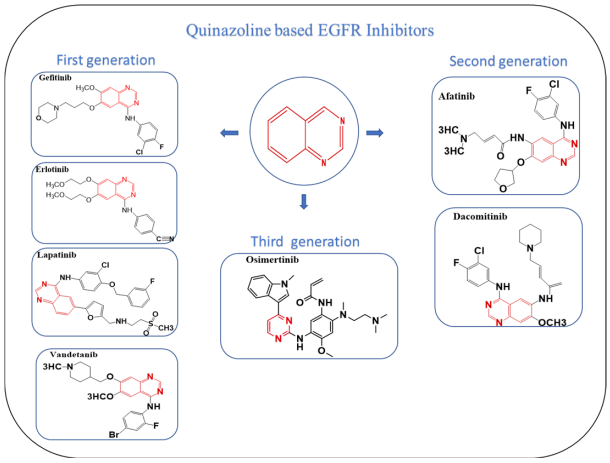


Figure 1. Structure of clinically approved EGFR inhibitors

EGFR exhibits a secondary mutation where the amino acid threonine at position 790 replaced by bulkier methionine in the amino acid chain. This substitution creates steric hindrance in the binding site of the EGFR TKI, posing a significant challenge for drug design. Initially, first-generation EGFR TKIs were developed, but they quickly encountered resistance from the T790M mutation. Second-generation EGFR inhibitors, although effective against the mutation, often caused severe adverse effects like grade 3 diarrhoea and skin rashes due to their affinity for binding with wild-type EGFR. Consequently, their dosage was limited due to toxicity concerns. To address these issues, third-generation EGFR inhibitors were designed and developed. These inhibitors selectively target drug-resistant oncogenic mutant EGFR T790M while minimizing side effects on wild-type receptors. They achieve this by binding irreversibly and covalently to cysteine at position 797. However, resistance to third-generation inhibitors has emerged, primarily through a new point mutation called C797S, which plays a crucial role in drug binding [7]. Over the past few years, numerous researchers have focused on designing and synthesizing more potent derivatives of quinazoline as EGFR inhibitors. The objective is to minimize resistance and overcome the limitations of currently available drugs while maintaining efficacy.

4-Amino quinazoline

4-aminoquinazoline (Figure 2) significant efficacy as an EGFR inhibitor in various cancer cell lines. Its potential as a kinase inhibitor makes it a promising candidate for targeted treatment of breast, lung, colon, and prostate cancer [8].

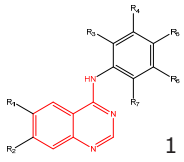


Figure 2. General structure of 4-aminoquinazoline

In recent years, 4-aminoquinazolin derivatives (Figure 3) used as kinase inhibitor as anticancer agent. Debases *et al.*, discussed development of number of 4-aminoquinazolin derivatives and identified as potent EGFR inhibitor against cancer cell lines and maximum compounds showed IC_{50} value less than 10 nM. Analysis of Optimal binding conformation was done by docking study that would position the most potent compound within the active pocket of EGFR. 4-aminoquinazolines targeting various proteins such as EGFR, HER2, and VEGFR which have been utilized as kinase inhibitors. These compounds have exhibited significant biological activities against numerous cancer types, including breast cancer, colon cancer, non-small cell lung cancer (NSCLC), hepatic cancer and stomach cancer. The compounds displayed notable antiproliferative effects on H358 and A549 cells, which possessed outstanding kinase inhibitory properties against both EGFRwt and EGFRT790 M/L858R mutations.

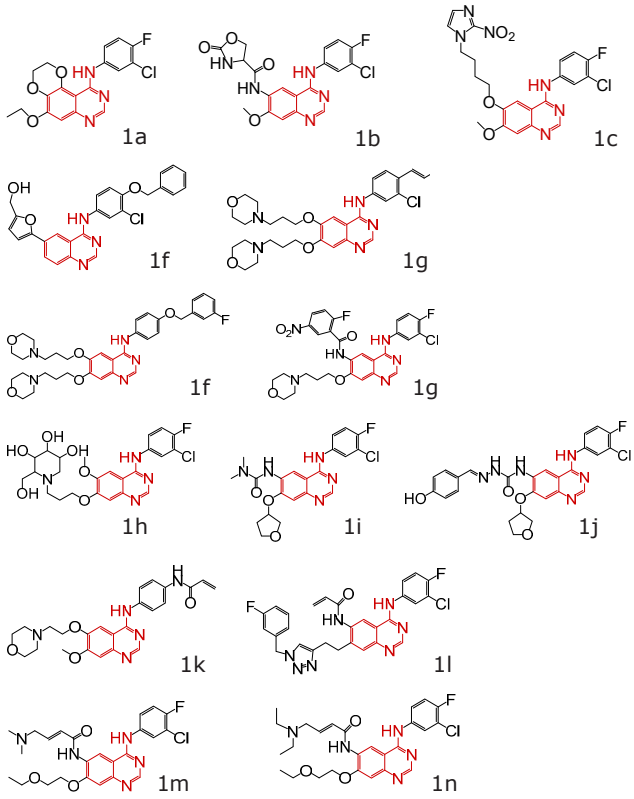


Figure 3. 4-aminoquinazoline analogues

Tu *et al*. reported that Compounds 1i and 1j, which are quinazoline derivatives containing a semicarbazone moiety, demonstrated significant inhibition of EGFR in multiple cancer cell lines including A549, HepG2, MCF-7, and PC-3. The reported IC_{50} values for compound 1i were 0.05 nM, while for compound 1j they were 0.1 nM, indicating their strong inhibitory potential against EGFR (Table 1). In-depth investigation into the structure-activity relationship (SAR) uncovered that the inclusion of a hydroxy group at position C-4 had a notable impact on the activity. Additionally, substituting the tetrahydrofuran group with a methyl moiety did not enhance the compounds' activity [21].

Table 1. IC_{50} values (in nm) of 4-aminoquinazoline analogues as inhibitors of EGFR and HER

Inhibitors	EGFR	HER2	Standard used	Reference
1a	2.0		Erlotinib	9
1b	26.33		Gefitinib	10
1c	0.4		Gefitinib	11
1d	5.0		Gefitinib	12
1e	20.0		Lapatinib	13
1f	7.0		Lapatinib	14
1g	5.0		Gefitinib	15
1h	1.7		Miglitol	16
1i	0.05		Afatinib	17
1j	0.1		Afatinib	18
1k	105		Gefitinib	19
1l	68	290	Gefitinib	20
1m	0.6	42.2	Afatinib	21
1n	1.4	10.9	Afatinib	21

4-Anilinoquinazoline

Zhang-Hai-qi *et al*. developed number of compounds called 4-anilinoquinaquinazoline analogues. These analogues consist of either a glycine methyl ester or diaryl urea component which is inhibitors of both VEGFR-2 and EGFR (Figure 4) [22]. Among these analogues, IC_{50} values of compounds 3a, 3b, and 3c was found to be 1nM, 78nM, and 51nM, respectively (Table 2), which was demonstrated the highly potent EGFR inhibitors [23].

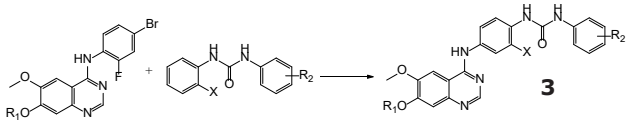
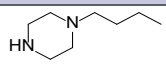
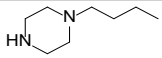
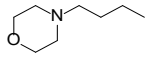


Figure 4. Design of hybrid scaffold based upon 4-anilinoquinazoline 3a-c

Table 2. 4-anilinoquinazoline analogues

Compound	X	R1	R2
3a	*Cl*		*m*-CH3, *p*-CH3
3b	*Cl*		*m*-Cl, *p*-F
3c	*Cl*		*m*-CH3, *p*-CH3

Compounds (3a, 3b, 3c) demonstrated outstanding inhibitory potencies due to the presence of chlorine in the urea group's ortho-position and the modification of the terminal diaryl urea (-ArNHCONHAr) moiety.

Quinazolin-4(3H)-one

Hazem A. Mahdy developed and produced novel variations of quinazoline 4(3H)-one compounds that include additional components such as 1, 6-dihydropyrimidine, thiazolidine-4-one, sulphonamide, sulfonylurea, thiazolidine 2, 4-dione, pyrano-thiazole, semicarbazone, thiosemicarbazone or oxime groups. These components are connected with diverse linker (spacer) molecules as shown in (Figure 5) [24].

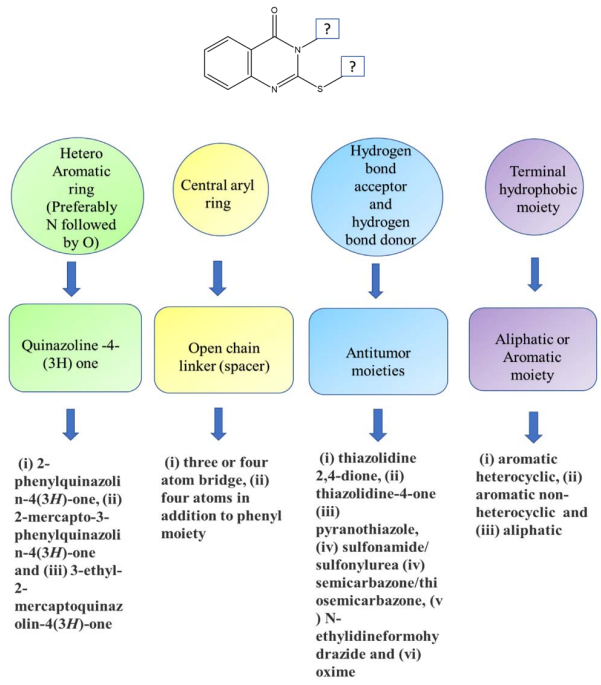


Figure 5. Structural modification of Quinazolin-4(3H)-one as effective EGFR inhibitors

It has been reported that Quinazolin-4(3H)-one through molecular hybridization with other effective antitumor components at the second position yields more effective inhibitory activities as compared to third position substitution after structure modification (Figure 6). When a 2-sulfanylquinazolin-4(3H)-one is substituted at the 3-position, the introduction of an aliphatic ethyl group demonstrates better biological activity than an aromatic phenyl group. At the 2-position, thiosemicarbazone or semicarbazone moieties exhibit higher potency than sulfonylurea moieties [25-28]. Based on these considerations, Quinazolin-4(3H)-one hybridized derivatives were designed and synthesized.

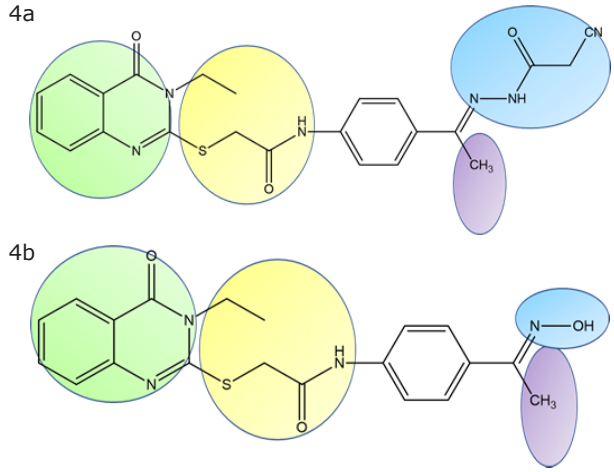


Figure 6. Hybrid derivative of sulfanylquinazolin-4-(3H)-one

The IC50 values for compound 4a were reported as 13.79 µm, 8.35 µm, 11.87 µm, and 8.35µm against MCF-7, HCT-116, and HEPG-2 cells, respectively. For compound 4b, the IC_{50} values were 3.97 µm, 4.83 µm, and 4.58 µm against HEPG-2, HCT-116, and MCF-7 cells, respectively, which shows that compound 4a and 4b exhibited high potency against all above four cancer cell lines.

Triazole substituted quinazoline

1, 2, 3-Triazole is a significant pharmacophore with valuable anticancer properties due to its capability to establish hydrogen bonds with biological targets. [29]. Both 1, 2, 3-triazole and quinazoline are crucial components as EGFR inhibitors in anticancer applications [30]. Banerji *et al.* Developed and synthesized hybrid analogues incorporating triazole-substituted quinazoline for targeting EGFR tyrosine kinase and evaluating their anticancer activity (Figure 7) [31]. The most analogues exhibited effective inhibition of EGFR and demonstrated moderate to good potency in inhibiting the proliferation of various cell lines of cancer (HCT116, MCF-7. HEPG and PC-3).

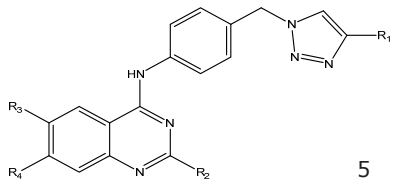


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Figure 7. Triazole substituted Quinazoline

Table 3. Triazole substituted analogues as EGFR TK inhibitors

Compound	R1	R2	R3	R4
5a		H	OMe	OMe
5b		Cl	OMe	OMe
5c		H	H	H
5d		H	OMe	OMe
5e		Cl	OMe	OMe
5f		H	H	H
5g	OH	H	OMe	OMe
5h	OH	Cl	OMe	OMe
5i	OH	H	H	H
5j	O	H	OMe	OMe
5k	O	Cl	OMe	OMe
5l	O	H	H	H
5m	HN	H	OMe	OMe
5n	HN	Cl	OMe	OMe
5o	HN	H	H	H
5p		Cl	H	H
5q		Cl	H	H
5r	OH	Cl	H	H
5s	O	Cl	H	H
5t	HN	Cl	H	H

The IC_{50} value of compound 5b (Table 3) was found to be 20.71 µM, hence, showed superior potency to the standard, Erlotinib (11.57 µM). This suggests that it has the potential to be a potent drug. Moreover, it was also observed that the –OMe (methoxy) group at the 6th and 7th positions and the chlorine atom at the 2nd position of quinazoline may increase its anticancer activity due to a structural activity relationship. Compounds having substitution of the −Cl atom at the second position of quinazoline (5b, 5e, 5h, 5k, and 5n) and an -OMe group at 6, 7 positions were found to be superior as compared to other substituents – and also to be more active.

Pyrimidine scaffolds as EGFR kinase inhibitors

A number of pyrimidine-based pharmacophore has shown good antiproliferative activity [32]. Based on SAR study of 2-anilidopyrimidine, 4th position of 2-anilidopyrimidine substituted by hydrazine functionalities and pyrazolone ring exhibited superior activities (Figure 8) [33,34].

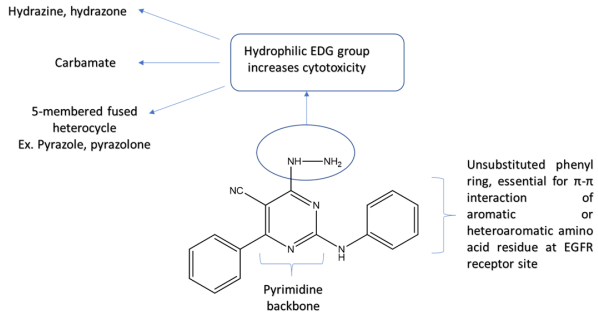


Figure 8. Design strategy for targeted Pyrimidine analogues

Aboulwafa *et al.* aimed to enhance the EGFR inhibitory activity by designing and synthesizing derivatives of 2-anilinopyrimidine. They incorporated hydrazolone and pyrazolone at the 4th position of the 2-anilinopyrimidine structure (Figure 9). These compounds that were synthesized and subjected to evaluation of their IC_{50} values using MTT assay. In the MCF-7 cell line, the majority of the compounds demonstrated IC_{50} values between 0.27 and 10.57 µm, when compared to the reference drug 5-FU with an IC_{50} value of 10.80 µm [35].

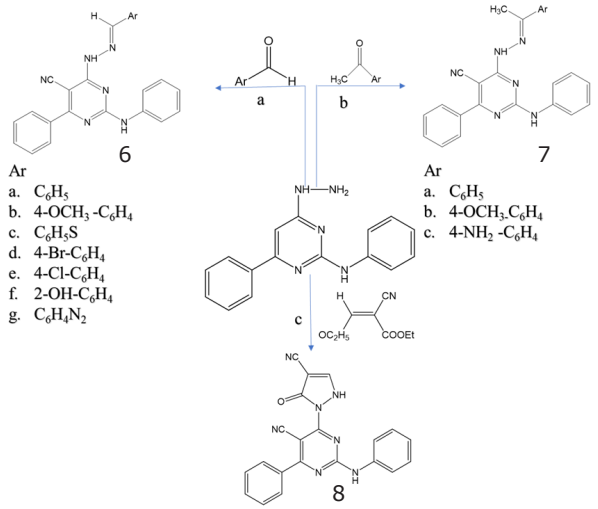


Figure 9. Synthetic pathway to hydrazone 6a-g and 7a-c, pyrazolyl-pyrimidine 8

The study concluded that compound 6c, 7b and 8 serves as important gateway for designing and targeting for new multitarget anticancer which act as good inhibitor of EGFR as compared to reference 5-FU, with superior anticancer activity against the two tested breast cancer cell lines (MDA-MB-231 and MCF-7. Furthermore, The compounds were found to exhibit strong binding affinities to the target EGFR enzymes, as revealed by docking studies [36,37].

Souad A. Elmetwally *et al*. developed and synthesized range of thieno [2,3-d] pyrimidine derivatives as potent dual tyrosine kinase inhibitors targeting EGFR and HER2, aiming to combat diverse cancer cell lines (HCT-116, HepG2, A431, and MCF7) (Figure 11) [38]. The choice of a heteroaromatic ring system at the first position was based on important bio-isosteric considerations for the quinazoline moiety by using the thieno [2, 3-d] pyrimidine moiety as a bio-isostere. The spacious adenine binding region of EGFR-TK is effectively occupied by the bicyclic structure of the thieno [2,3-d] pyrimidine ring. [39]. The nitrogen heteroatom present in the ring acts as a hydrogen-bond acceptor, contributing to excellent EGFR-TK potency [40]. For the second position, a variety of hydrophobic heads such as (substituted) phenyl, aromatic, and fused aromatic heterocyclic structures were selected. The third position functioned as the linker (spacer) region, where –NH compounds used for modifications in length and the presence of hydrogen acceptor and/or donor groups were alsomade. As for the fourth position, a hydrophobic tail was introduced, and a cyclohexyl group was added at position 2,3-d of the thiopyrimidine nucleus to effectively occupy the front hydrophobic region of the ATP binding site of EGFR-TK (Figure 10).

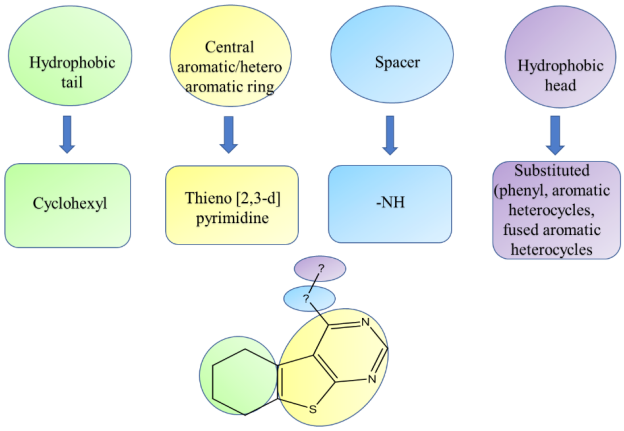


Figure 10. The pharmacophoric characteristics of thieno [2,3-d] pyrimidine as inhibitors of EGFR-TK

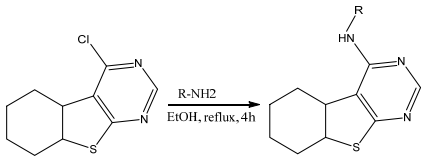
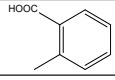
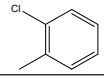
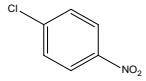
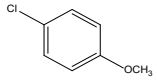
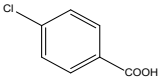
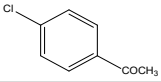
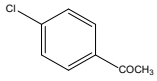
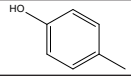
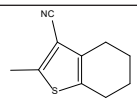
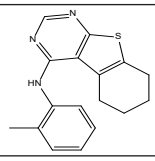
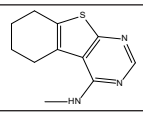


Figure 11. Synthetic pathway to Thieno [2,3-d] pyrimidine analogues

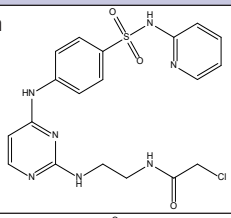
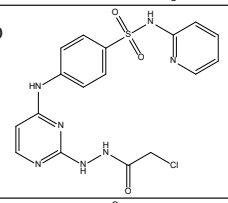
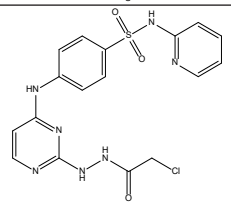
Table 4. Thieno [2, 3-d] pyrimidine analogues as EGFR Inhibitors

Compound	R	IC_{50}(μM)			
		HePG2	HCT-116	MCF-7	A431
9a		87	71	81	-
9b		36	40	46	-
9c		85	64	77	-
9d		42	26	25	-
9e		67	62	75	-
9f		35	50	53	-
9g		26	16	23	16
9h		13	10	12	47
9i		27	30	37	13
9j		70	90	95	-
9k		7	50	7	9

The compounds were evaluated for their inhibitory action with comparison to erlotinib as standard against different cancer cell lines (HepG2, MCF-7, HCT-116 and A431) (Table 4). It was observed that three compounds (9g, 9h, and 9k) revealed excellent inhibitory effects, exhibiting IC_{50} values spanning from 7.592±0.32 to 16.006±0.58 μM. Furthermore, structural activity investigations demonstrated a preference for substituting the terminal hydrophobic head with a less bulky electron-donating group. Compound 9k, which had a longer linker and hydrophobic head, showed particularly enhanced activity.

In a study by Harun Patel *et al*, a series of reversible non-covalent T790M EGFR inhibitors, specifically 2, 4-disubstituted aminopyrimidines, were designed and synthesized. Osimertinib commonly causes cardiotoxicity as an adverse effect [41]. Among the virtually sorted compounds, compound 10a and 10b were identified as the most active compounds against the double mutant L858R/T790M EGFR, with IC_{50} values of 0.56 and 0.62 μm in enzymatic assays, and 0.88 and 0.92 μm in cellular assays (Table 5). The compounds with flexible substituents at the second position demonstrated enhanced anti-tumour activity and an improved pharmacokinetic profile with minimal cardiotoxicity [42].

Table 5. Activities of disubstituted aminopyrimidine

Compound	NCI-H197(EGFR L858R/ T790M) IC_{50} (μM) (Cellular assay)	NCI-H197(EGFR (L858R/T790M) IC_{50} (μM) (Enzymatic assay)
10a 	0.88	0.56
10b 	0.92	0.62
 Osimertinib	0.019	0.012

Eman Z. Elrazaz conducted an investigation on the effects of substituting various groups on thieno[2,3-d] pyrimidine scaffolds and evaluated their antiproliferative activity by inhibiting EGFR [43]. A series of 4-N-substituted-6-aryl-thienopyrimidines were assessed for their efficacy as EGFR inhibitors. The structure-activity relationship analysis indicated that the potency of the compounds depended on the substitution at different positions in the 6-aryl group. The activity increased when a hydroxymethyl group was substituted at the meta or para position, as it facilitated hydrogen bonding with the Asp residue in the Asp-Phe-Gly motif of the receptor sites [44]. This substitution led to the discovery of three active compounds, namely (R)-11a, (S)-11b, and (S)-11c, with an effective EGFR IC50 value of <1 nM (Figure 12) [45].

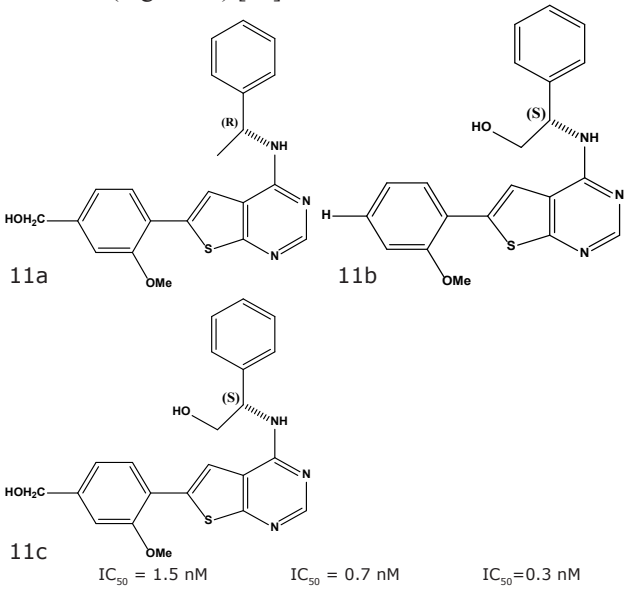


Figure 12. Design of 1,6-napthyridinone derivatives bearing quinoline moiety

Quinolines as EGFR inhibitors

Extensive enzyme-based studies were conducted to investigate the structure-activity relationship and evaluate pharmacokinetic evaluation parameters of quinolines (Figure 13). A new series of N-substituted-3-phenyl-1,6-naphthyridinone derivatives of quinoline were designed, synthesized, and assessed for their high selectivity to EGFR. [46].

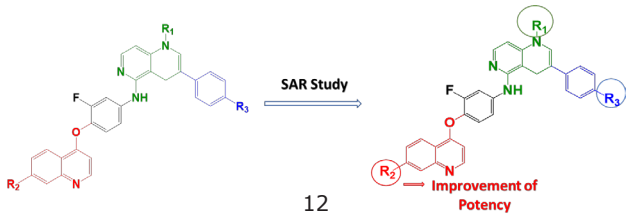


Figure 13. Design of 1,6-napthyridinone derivatives bearing quinoline moiety

The SAR study reveals the significance of the 1, 6-naphthyridine moieties as a key pharmacophoric group for demonstrating c-Met inhibition. Furthermore, the functionalization of the N (1) amine group in the 1, 6-naphthyridin-4(1H)-one moiety was shown to enhance selectivity [47,48]. The quinoline moiety has been established as a recognized scaffold for type II c-Met inhibitors, as it possesses favorable drug-like properties. Moreover, optimization of substituents in the quinoline fragment was found to have the potential to improve potency. Hence, synthesized derivatives of 1, 6-naphthyridone-based c-Met kinase inhibitors, incorporating a quinoline moiety, exhibit optimal c-Met potency. These derivatives have been selected as the starting material for further research to strengthen their potency and selectivity for anticancer activity (Table 6).

Table 6. Quinoline substituted analogues as c-Met and VEGFR-2 kinase inhibitor

Compound	R1	R2	R3	IC_{50}nM	
				C-MET	VEGFR-2
12a	Me	OMe	F	32.5	>3000
12b	Et	OMe	F	29.1	>3000
12c	i-Pr	OMe	F	58.7	>3000
12d	H	OMe	F	41	>3000
12e	H	OMe	F	31.2	>3000
12f	Me		F	35.6	>3000
12g	Me		F	22	>3000
12h	Me		F	12.7	>3000
12i	Et		F	9.5	>3000
12j	i-Pr		F	44.6	>3000
12k	H		F	58.7	>3000
12l	H		F	22.4	>3000
12m	H		F	76.1	>3000
12n	H		F	40.0	>3000
12o	H		F	41.0	>3000
12p	Bn		F	40.3	>3000
12q	H		F	117.2	>3000
12r	Me		H	10.6	>3000

Of the derivatives listed in Table 6, compound 12r indicated promising selectivity against VEGFR-2 and demonstrated excellent inhibitory activity against tumour growth. Therefore, it holds potential as a new lead molecule for selective type-II c-Met inhibitors.

Indole derivatives as EGFR inhibitors

The ongoing problem with marketed EGFR inhibitors is the development of resistance, often caused by the heterodimerization of EGFR with PDGFR-β, which neutralizes the inhibitor's activity against EGFR. To address this issue, Fischer et.al. designed and synthesized derivatives of pyrimido [4, 5-b] indoles with various substitution patterns at the 4-anilino position in order to enhance their potency against EGFR inhibitory activity (Figure 14) [49].

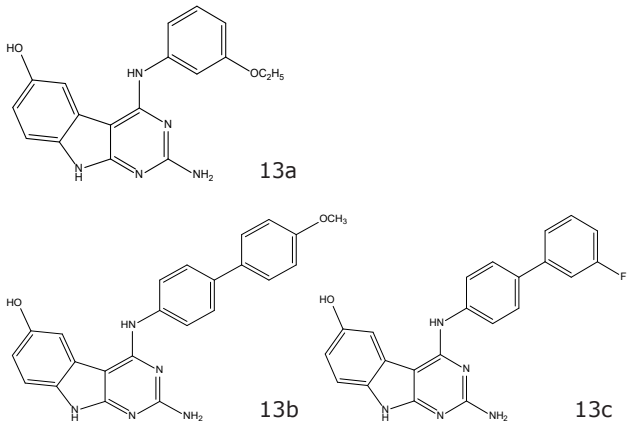


Figure 14. Pyrimido [4, 5-b] indoles derivatives

Of these, compound 13a demonstrated a significant improvement in EGFR inhibitory growth rate compared to erlotinib. In NSCLC cell lines, the EGFR inhibitory growth rate was enhanced from 32% to 71%, while in prostate cancer cell lines, it increased from 25% to 51%. In comparison, erlotinib exhibited an EGFR inhibitory growth rate of 20% in NSCLC cell lines and 40% in prostate cancer cell lines. This indicates that compound 13a possesses enhanced potency in inhibiting EGFR activity in both NSCLC and prostate cancer cell lines. Because secondary acquired mutation in EGFR i.e. EGFR T790M, form key components of resistance in NSCLC, Pankaj Kumar Singh *et al.,* created derivatives of indole pyrimidine scaffolds that were substituted with different aryl substitution (Table 7). Diverse derivatives were sketched based on molecular dynamic simulation studies and designed molecules were synthesized and evaluated against EGFR TK.

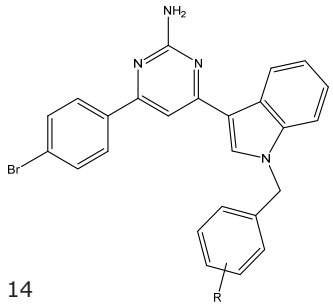


Figure 15. Indole pyrimidine derivatives

Table 7. Indole pyrimidine scaffolds as EGFR inhibitor

14a	4-methyl
14b	4-isobutyl
14c	4-isopropyl
14d	3-trifluoromethyl
14e	4-methyl
14f	4-fluoro
14h	4-chloro

Of these derivatives listed in Table 7, compounds 14a and 14c exhibited potent inhibitory activity in the nanomolar range (IC_{50}) against EGFR with the T790M mutation. These molecules also demonstrated dual inhibitory effects, indicating their ability to target multiple pathways. Additionally, compound 14h displayed notable inhibitory potential against secondary acquired EGFR and c-MET, with an IC_{50} value of 0.101 mM [50].

Miscellaneous Heterocyclic analogues as anticancer

Overall, heterocyclic moiety always be core part for development of anticancer **agent.as?** it contains exciting medicinal properties. Despite of several anticancer agent available, new more heterocyclic moieties have discovered due to its effective anticancer activity.

Thiazolyl-pyrazolines

The study conducted by Sever *et al*. focused on the synthesis and evaluation of hybrid thiazolyl-pyrazoline derivatives as potential cytotoxic agents and inhibitors of EGFR (epidermal growth factor receptor) and HER-2 (human epidermal growth factor receptor 2) (Figure 15). The researchers screened these derivatives for their cytotoxic effects on three cancer cell lines: MCF-7 human breast adenocarcinoma, A549 human lung adenocarcinoma, and A375 human melanoma [51].

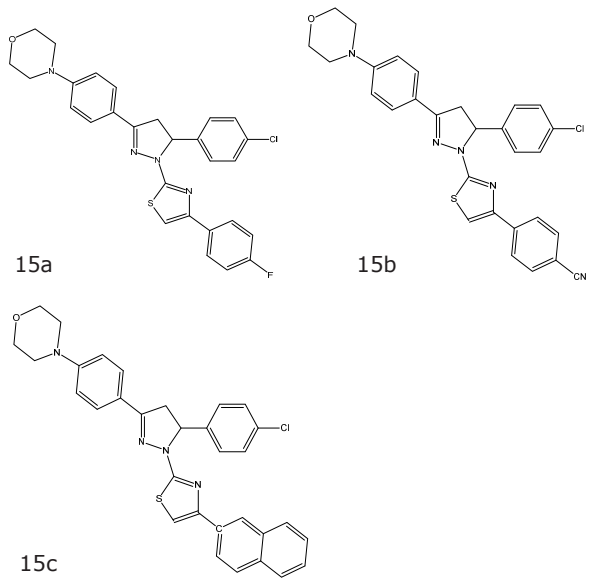


Figure 16. Thiazolyl-pyrazoline derivatives as EGFR inhibitor

According to the results reported in the study, compounds 15a, 15b and 15c exhibited significant apoptotic effects on both A549 and MCF-7 cell lines. Additionally, they showed

inhibitory potency against EGFR, surpassing the activity of erlotinib, a known EGFR inhibitor. Compound 15b and 15c demonstrated superior inhibitory activity against EGFR with IC_{50} values of 4.34± 0.66μM and 4.71±0.84μM respectively in comparison to erlotinib (IC_{50} =0.05±0.01μM). These compounds induced apoptosis in both EGFR and HER2 cell lines.

Molecular docking studied were also performed to gain insight into the binding interaction of compound 15b. The results revealed that it exhibited favourable binding affinity towards the ATP binding site of EGFR, interacting appropriately with the site. Additionally, compound 15b was found to be fit well with HER2 binding site, indicating its potential as a dual inhibitor of EGFR and HER2.

Overall, findings suggest that compounds 15b and 15c hold promise as dual inhibitor of EGFR and HER2. Their apoptotic effects and superior inhibitory activity against EGFR make them potential candidates for further development as anticancer agents.

Fused pyrazoles

Pyrazole and fused pyrazole systems, including pyranopyrazole and pyrazolpyrimidines, have shown promise as scaffolds for the development of anticancer agents [52-54]. El. Gazzar *et.al.* Synthesized fused pyrazole derivatives and assessed their *in vitro* anticancer activity as EGFR inhibitors (Figure 16). Compound 16 exhibited significant anticancer activity against EGFR, with an IC_{50} value of 0.06 μm. Moreover, compound 17 demonstrated *in vitro* anticancer activity against both EGFR and VEGFR. The potency of these compounds was further supported by docking studies, which revealed favourable interactions within the active sites of the enzymes [55].

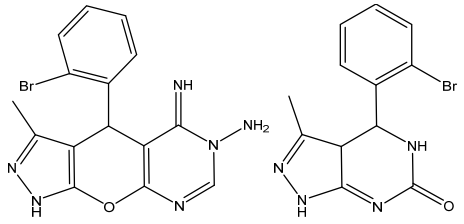


Figure 17. Fused pyrazole derivative as EGFR inhibitor

1,3,4-oxadiazole/chalcone hybrids

Marval Ali *et al*. conducted the design and synthesis of a novel series of hybrids incorporating 1, 3, 4-oxadiazole/chalcone moieties (Figure 17). These were characterized using various spectroscopic methods. The compounds exhibited potent anticancer activity, particularly against leukemia, and were further evaluated as inhibitors of EGFR, Src, and IL-6.

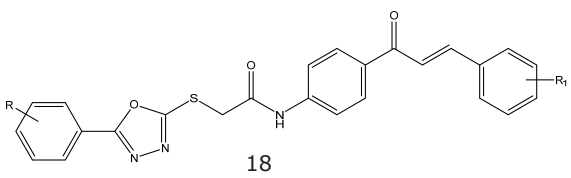


Figure 18. Hybrid 1, 3, 4-oxadiazole-chalcone derivatives

Table 8. 1, 3, 4-oxadiazole/chalcone analogues as EGFR Inhibitor

Compound	R	R1	Compound	R	R1
18a	H	H	18m	4-OCH_3	3,4-di-OCH_3
18b	H	4-Cl	18n	4-OCH_3	3,4,5-tri-OCH_3
18c	H	3,4-di-OCH_3	18o	3,4-di-OCH_3	H
18d	H	3,4,5-tri-OCH_3	18p	3,4-di-OCH_3	4-Cl
18e	4-Cl	H	18q	3,4-di-OCH_3	4-OCH_3
18f	4-Cl	4-Cl	18r	3,4-di-OCH_3	3,4-di-OCH_3
18g	4-Cl	4-OCH_3	18s	3,4-di-OCH_3	3,4,5-tri-OCH_3
18h	4-Cl	3,4-di-OCH_3	18t	3,4,5-tri-OCH_3	H
18i	4-Cl	3,4,5-tri-OCH_3	18u	3,4,5-tri-OCH_3	4-Cl
18j	4-OCH_3	H	18v	3,4,5-tri-OCH_3	4-OCH_3
18k	4-OCH_3	4-Cl	18w	3,4,5-tri-OCH_3	3,4-di-OCH_3
18l	4-OCH_3	4-OCH_3	18x	3,4,5-tri-OCH_3	3,4,5-tri-OCH_3

As shown in Table 7, among the compounds tested, compounds 18a, 18n and 18v demonstrated the strongest cytotoxic activity as EGFR inhibitors, with IC_{50} values ranging from 0.24 to 2.35 μM. For Src inhibition, these compounds exhibited IC_{50} values of 0.96 to 6.24 μM. Additionally, Compound 18v displayed significant inhibitory activity against IL-6, with control percentages ranging from 20% to 23%. Notably, Compound 18v revealed the strongest cytotoxic activity overall [56].

CONCLUSION

This review extensively discusses various heterocyclic scaffolds and their analogues as effective inhibitors of EGFR. The synthetic strategies employed for the development of different heterocyclic analogues, along with their structure-activity relationship studies, highlight the significant role of heterocyclic pharmacophores in medicinal drug discovery. These compounds have shown promising *in vitro* anticancer activities, specifically targeting non-small cell lung cancer (NSCLC), colon cancer, and breast cancer. Examples of heterocyclic compounds with demonstrated EGFR kinase inhibition include 4-aminoquinazoline, quinazolin-4(3H)-one, triazole-substituted quinazoline, thieno [2, 3-d] pyrimidine, disubstituted aminopyrimidine, quinoline, indole, thiazolyl-pyrazoline, fused pyrazole, and 1, 3, 4-oxadiazole/chalcone hybrid analogues. The exploration of heterocyclic compounds for EGFR inhibition continues, with the aim of identifying even more potent inhibitors in the future. This comprehensive article provides valuable information for medicinal chemists, emphasizing the importance of heterocyclic scaffolds and their potential as pharmacophores for EGFR inhibitors and future cancer therapies.

FUNDING

This review article did not receive any specific funding for its publication.

CONSENT FOR PUBLICATION

All authors listed above have reviewed the final version of this review article and have given their consent for its publication in the Current Issues in Pharmacy and Medical Sciences

COMPETING INTERESTS

There are no conflicts of interest among the authors

ETHICAL APPROVAL

This review article did not involve primary research or the collection of data from human subjects. Therefore, ethical approval was not required.

ACKNOWLEDGEMENT

The authors have no specific acknowledgments for the publication of this review article

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