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REVIEW

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors for the treatment of non-small cell lung cancer: a patent review (2014-present)

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ABSTRACT

Introduction: EGFR is the receptor for epidermal growth factor (EGF) and belongs to the protein tyrosine kinase (PTK) receptor. It is closely related to the inhibition of tumor cell proliferation, invasion, and apoptosis. Overexpression or mutation activation of EGFR is involved in the development of many human malignancies, especially non-small cell lung cancer (NSCLC). At present, numerous small molecule tyrosine kinase inhibitors (TKIs) have been developed to target the ATP-binding region of EGFR, aiming to develop selective and effective inhibitors for the treatment of NSCLC against EGFR mutants.

Areas covered: This review covers the latest progress in the patented EGFR inhibitors and the inhibition activity against NSCLC from 2014 to present.

Expert opinion: EGFR is an important anti-tumor target, and small molecule inhibitors targeting EGFR have become important biologically active compounds for the treatment of cancer, especially against NSCLC. Among the recent patents available, great majority of them focus on selective inhibitors of EGFR mutants. Although great achievements have been made in the development of selective EGFR inhibitors, there is still an urgent need to discover new EGFR inhibitors which are safe, efficient, selective, and low-toxic to avoid the adverse pharmacokinetics caused by wild-type EGFR feature.

1. Introduction

Lung cancer remains the most common and deadliest disease on record. According to data from the World Health Organization, approximately 2.09 million new cases are reported annually, and 1.76 million lung cancer deaths worldwide each year (18.4% of all cancer deaths) [1,2].

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, with increasing incidence each year over the world, seriously threatening human health [3]. For advanced patients, although radiotherapy and chemotherapy can improve the survival rate to a certain extent, they are also highly toxic to normal cells in the human body, resulting in decreased immunity, bone marrow suppression, neurotoxicity, and other difficult side effects [4,5]. Molecular targeted therapy has gradually become a new choice because of its low dosage, remarkable effect, strong specificity, and low side effects [6]. Therefore, there is an urgent need for therapeutic agents that can specifically target key genes related to tumor growth.

Protein tyrosine kinases (PTKs) can catalyze the phosphorylation of a variety of important tyrosine residues and activate functional proteins. Based on their structural characteristics, they can be divided into receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (NRTKs) [7]. Among them, RTKs include epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth

factor receptor (VEGFR), etc., which can be used as receptor proteins or enzymes that bind to ligands while catalyzing the phosphate residues of target protein ATP [8].

Epidermal growth factor receptor (EGFR), which is a transmembrane protein tyrosine kinase member of ErbB receptor family, also known as ErbB1 or HER1 [9,10]. When combined with growth factor ligands, such as epidermal growth factor (EGF), it can form homodimers, or form heterodimers with other members of the family, such as ErbB2 (HER2), ErbB3 (HER3) or ErbB4 (HER4) [11,12], further activating the intracellular region and bind to ATP molecules. When the phosphate residues on ATP are catalyzed, they activate downstream signaling, which in turn transmit signals into the cell and regulates cell growth, adhesion, survival, migration, proliferation, and differentiation [13,14]. Aberrantly expressed EGFR is closely associated with tumor invasion and metastasis, tumor angiogenesis, chemoresistance, and dysregulated cell proliferation [15]. Notably, overexpression and mutations of EGFR have been found in patients with non-small cell lung cancer [16]. Therefore, the phosphorylation of downstream signals can be effectively controlled by inhibiting the expression of EGFR, thereby inhibiting the proliferation of tumor cells. Numerous clinical experimental research results have shown that small molecule inhibitors targeting EGFR showed excellent therapeutic effects for NSCLC treatment. Consequently, research and development of anti-non-small cell lung cancer drugs targeting EGFR has become a hotspot.

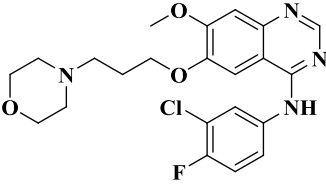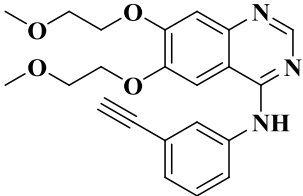## 2. Driver mutations in EGFR and EGFR-TKIs in clinical development

Small molecule EGFR tyrosine kinase inhibitors (EGFR-TKIs) compete with ATP to bind to the phosphorylation sites in the intracellular domain of EGFR, inhibiting the autophosphorylation process of EGFR and blocking the downstream signal pathway, then achieve the purpose of inhibiting tumor cells [17]. Therefore, various small molecule inhibitors targeting EGFR have been developed and evaluated as drugs for the treatment of non-small cell lung cancer (Table 1). Depending on the site of action of EGFR inhibitors, they were divided into 4 categories.

The first generation of EGFR tyrosine kinase inhibitors were developed for the therapy of EGFR activating mutation-positive NSCLC patients with a substitution mutation in exon 21 (L858R) where the 858th amino acid was changed from leucine to arginine and exon 19 deletion (delE746-A750, del19) [18]. They were all reversible inhibitors containing quinazoline structure. Gefitinib, developed by AstraZeneca, was approved by the FDA for marketing in 2003, for the treatment of patients with locally advanced or metastatic NSCLC, which inhibited wild-type EGFR to a less extent [19]. Developed by Roche Pharmaceuticals, erlotinib selectively blocked the EGFR downstream signaling pathway, thereby inhibiting tumor cell proliferation. In 2004, the FDA-approved erlotinib for the treatment of locally advanced or metastatic NSCLC patients after failure of chemotherapy. Clinical trials had shown that it could prolong the survival time of patients [20,21]. Developed by Zhejiang Beda Pharmaceutical Co., the drug icotinib was safer than gefitinib, indicating that icotinib was suitable for patients with advanced NSCLC. It was approved for listing in China in 2011 [22]. Lapatinib, developed by Glaxo Smith Kline and approved by the FDA in 2007, was a dual inhibitor of EGFR and ErbB2 for the therapy of HER2 overexpressing metastatic breast cancer [23]. The first generation of EGFR tyrosine kinase inhibitors showed good therapeutic effects in the early treatment of NSCLC. However, after 12 months of clinical treatment, EGFR was further mutated, and 50–60% of patients have acquired varying degrees of drug resistance, and even increasing the dose of the drug could not achieve a good therapeutic effect [24]. The main one was the T790M mutation, in which the threonine at the 790th amino acid position was changed to methionine [25]. Compared with Thr790, Met790 was larger and less polar. Therefore, when the first-generation EGFR inhibitors bound to the mutated EGFR kinase, the large volume of Met790 blocked the binding of the small molecule inhibitor to the kinase binding site, which rendered the inhibitor ineffective [26]. In addition, the presence of T790M increased the affinity of EGFR to ATP, which reduced the affinity of EGFR inhibitors to EGFR tyrosine kinases [27,28].
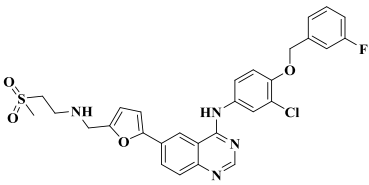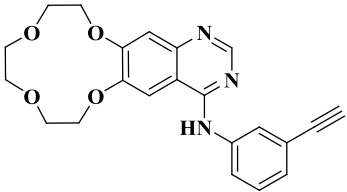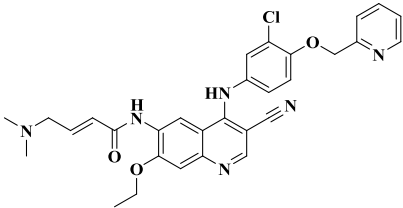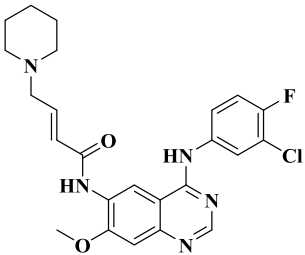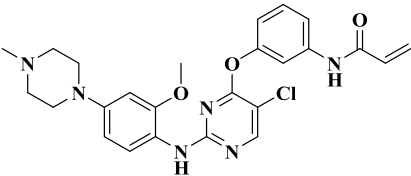
The second-generation EGFR inhibitors were developed to overcome the drug resistance problem of $EGFR^{T790M}$ mutation. Most of them retained the 4-aminoquinazoline structure of the first-generation EGFR inhibitors, and introduced acrylamide unsaturated groups, which could form a covalent connection with cysteine 797 (Cys797) [29]. Therefore, they were transformed into potent and durable irreversible inhibitors. Afatinib, developed by Boehringer Ingelheim, was approved by the FDA in 2013. The drug

Table 1. EGFR tyrosine kinase inhibitors in clinical studies.

Drug	Structure	Target	Status	Company	CAS No.
Gefitinib (ZD1839)		EGFR	Launched (2003)	AstraZeneca	184,475–35-2
Erlotinib (CP358774)		EGFR	Launched (2004)	Roche	183,321–74-6

Table 1. (Continued).

Drug	Structure	Target	Status	Company	CAS No.
Lapatinib (GW572016)		EGFR HER2	Launched (2007)	GlaxoSmithKline	231,277–92-2
Icotinib (BPI2009)		EGFR	Launched (2011)	Betta Pharmaceuticals	610,798–31-7
Afatinib (BIBW2992)		EGFRHER2 HER4	Launched (2013)	Boehringer-Ingelheim	850,140–72-6
Neratinib (HKI272)		EGFRHER2 HER4	Launched (2017)	Wyeth Research	698,387–09-6
Dacomitinib (PF-299,804)		EGFR HER2 HER4	Launched (2018)	Pfizer	1,110,813–31-4
WZ4002		EGFR	Preclinical	Dana-Farber Cancer	1,213,269–23-8

(Continued)

Table 1. (Continued).

Drug	Structure	Target	Status	Company	CAS No.
Rociletinib (CO1686)		EGFR	termination	Clovis Oncology	1,374,640–70-6
Osimertinib (AZD9291)		EGFR	Launched (2015)	AstraZeneca	1,421,373–65-0
Olmutinib (HM61713)		EGFR	Launched (2016)	Hanmi Pharmace	1,353,550–13-6
EAI001		EGFR	Preclinical	Novartis	-
EAI045		EGFR	termination	Novartis	1,942,114–09-1

acts on multiple targets of EGFR, HER2, and HER4 simultaneously. It could effectively enhance the therapeutic effect in patients with EGFR^{del19}, EGFR^{L858R} and EGFR^{T790M} mutations [30]. However, in the later period of medication, most patients developed a dose-dependent manner, toxic side effects became more pronounced with increasing dosage. Dacomitinib was jointly developed by Pfizer and the University of Auckland and was approved by the FDA in 2018. Its target of action was the same as that of afatinib [31,32]. Neratinib developed by Wyeth Research was different from the former two inhibitors. The core structure of neratinib was 3-cyanoquinoline. Approved by the FDA in 2017, it was mainly used to treat HER2 metastatic breast cancer [33]. The second-generation inhibitors were multi-target inhibitors, so they had poor selectivity. Only at high concentrations could these TKIs showed activity against the T790M mutation, exceeding the patients' maximum tolerated dose [34]. They also had inhibitory

activity against wild-type EGFR, causing side effects such as diarrhea and rash. Therefore, improving the selectivity of EGFR inhibitors to mutant EGFR and reducing toxic side effects had become the primary goal of the next generation of EGFR inhibitors.

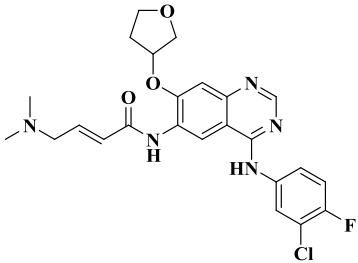The third-generation EGFR inhibitors were developed to solve the problem of poor selectivity of second-generation drugs. Their core structures were converted from 4-aminoquinazoline, which had a high affinity for EGFR^{WT}, to 2-aminopyrimidine, and the Michael acceptor acrylamide unsaturated group was retained. The first reported third-generation EGFR inhibitor WZ4002 could selectively inhibit EGFR$^{L858R/T790M}$ kinase, and its inhibitory effect on wild-type EGFR was 100 times lower than that of gefitinib [35]. Although WZ4002 had not entered clinical trials, its special structure provided reference and inspiration for the development of third-generation inhibitors. Rociletinib (CO1686), developed by Clovis Oncology, was an orally effective selective inhibitor of

EGFR. It was effective in NSCLC patients with T790M mutation [36]. However, in subsequent clinical treatment, most patients had intolerable side effects such as nausea, diarrhea, and hyperglycemia. Therefore, CO1686 was terminated by the FDA in clinical trials [37]. Osimertinib (AZD9291) with minimal toxicity and excellent selectivity to wild-type EGFR became the first globally recognized TKI for EGFR^{T790M}-positive NSCLC patients [38]. Its structure differed from the previous two in that it introduced *N*-methylindole, which penetrated deep into the hydrophobic cavity interior of the EGFR protein. In addition, it directly connected the Michael receptor acrylamide structure to aniline, which made the combination with Cys797 stronger. The modification of these two parts rendered AZD9291 high selectivity and low toxicity [39]. Olmutinib (HM61713), approved for marketing in 2016, was an irreversible thieno[3,2-*d*]pyrimidine inhibitor developed by Hanmi Pharmaceutical [40]. It could significantly improve the progression-free survival of NSCLC patients, and had little side effects. Nevertheless, clinical studies had shown that 20–30% of patients treated with third-generation EGFR inhibitors had a C797S point mutation where the amino acid at position 797 was mutated from cysteine to serine, which prevented the irreversible inhibitor from covalently binding to Cys797 [41]. The loss of covalent interaction led to a significant reduction in inhibition, which then led to the development of resistance. The EGFR^{C797S} mutation was identified as the main mechanism of resistance to third-generation inhibitors. It was reported that there were more resistance mechanisms, for example, the L718Q mutation represented another resistance mechanism to AZD9291. Therefore, it was possible to develop TKIs for this specific mutant [42].

The current generations of EGFR TKIs were aimed at the ATP site of kinases, and exerted their therapeutic effects by competing with ATP for the binding sites of kinases. However, it was very difficult to maintain the inhibitory activity against mutant EGFR while competing with ATP [43]. So allosteric inhibitors had been developed to solve this problem. Novartis Pharmaceuticals developed the first globally recognized fourth-generation EGFR inhibitor EAI045, which was modified based on EAI001 identified by screening with purified EGFR mutant kinase. The inhibitory active of EAI045 on EGFR$^{L858R/T790M}$ was stronger than EAI001 [44]. The crystal structure of EAI045 indicated that it bound to the allosteric site in the inactive conformation of EGFR kinase. However, in the activated state, the two subunits of the EGFR dimer receptor interacted in an asymmetric manner. Cetuximab could block the dimerization of EGFR and sensitized EGFR kinase to the denaturing reagent EAI045 [45,46]. Therefore, when combined with cetuximab, EAI045 had a significant inhibitory effect on EGFR$^{L858R/T790M/C797S}$. However, its inhibitory effect on EGFR^{del19} was not satisfactory, and it had not been able to enter clinical trials due to its poor safety [47]. The fourth-generation EGFR inhibitors needed to be further explored and improved.

3. Recent EGFR inhibitors in patents and scientific literature

Targeting EGFR to treat non-small cell lung cancer is a recognized goal. In the past 10 years, pharmaceutical companies and academic research groups have increased their efforts to develop small molecule inhibitors of different structures against different EGFR mutations. In this review, we mainly focus on the small molecules described of the patents (2014-present) available in English and Chinese. And the EGFR inhibitors described herein are discussed around the classification of their molecular structures.

3.1. Quinazoline derivatives as EGFR-TKIs

Most inhibitors containing quinazoline core structure show excellent dual inhibitory effects on EGFR and HER2, such as the marketed icotinib, afatinib, dacomitinib, and lapatinib. This section summarized these structures and some representative compounds were listed in Figure 1.

Compounds **1** and **2** in the patent **US2015065709A1** containing a 4-anilinoquinazoline core ring inhibited EGFR and HER2 with IC$_{50}$ values of 1.3 and 15 nM, as well as 0.4 and 11.7 nM, respectively, which also showed good pharmacokinetic parameters with low clearance, good oral absorption, long half-life and high tissue distribution in CD-1 mice [48]. The patent **CN103772371A** disclosed a series of 6-furyl quinazolin-4-amine compounds as dual inhibitor of EGFR and HER2. Compound **3** of them showed potent inhibition activity with IC$_{50}$ values of 15 and 6.3 nM against on EGFR and HER2, which were better than lapatinib (IC$_{50}$ = 21 and 8.5 nM). For human breast cancer cell lines BT-474 with high expression of HER2 receptor and human gastric cancer cell lines NCI-N87 with high expression of EGFR/HER2 receptor, compound **3** had IC$_{50}$ values less than 20 nM, exhibited high inhibitory activities against EGFR and HER2 [49]. The patent **CN108640928A** reported some compounds containing quinazoline core structure for the treatment of lung cancer with brain metastasis. In different species of liver particles, they possessed good metabolic stability, high permeability, strong intracellular penetration, and small efflux, which facilitated the penetration of the drug into the brain tissue, indicating that they had good therapeutic potential for brain metastases. Representative compound **4** showed marked inhibition activity against EGFR^{del19} as well as NSCLC cells PC-9 (expressing EGFR^{del19} gene), with IC$_{50}$ values of 0.052 nM and 5.34 nM, respectively. It was worth noting that it had a better antitumor effect than erlotinib in nude mice model of PC-9Lu in situ brain metastasis, which indicated that compound **4** had potential use in the treatment of brain metastases. In addition, it enhanced metabolic stability in rats and monkeys [50]. Patent **CN106008480A** revealed the capability of compound **5** containing 4-anilinoquinazoline core ring bearing different substituents on cinnamamide to inhibit proliferation in vitro of four cancer cell lines A549 (human non-small cell lung cancer, expressing EGFR^{WT} gene), PC-3 (human prostate cancer), MCF-7 (human breast cancer) and Hela (human cervical cancer), with the IC$_{50}$ values of 0.07, 7.67, 4.65, and 4.83 μM, which were equivalent to afatinib (IC$_{50}$ = 0.05, 4.10, 5.83, and 6.81 μM). It was further evaluated for the EGFR kinase inhibitory, the results showed that it equal to the reference compound afatinib (IC$_{50}$ = 1.6 nM), with the IC$_{50}$ values of 3.6 nM [51]. Compound **6** from **CN106866642A** similar in structure to compound **5** showed slightly lower activity toward EGFR kinase compared to the afatinib (IC$_{50}$ = 1.6 nM), with the IC$_{50}$ values of 56 nM. And there was apoptosis in A549 (EGFR^{WT}) cells treated with compound **6** [52]. Representative compounds **7** and **8** in the patent **CN108658946A** achieved strong EGFR$^{del19/L858R}$ inhibition and could inhibit the proliferation of NSCLC cell lines NCI-H3255
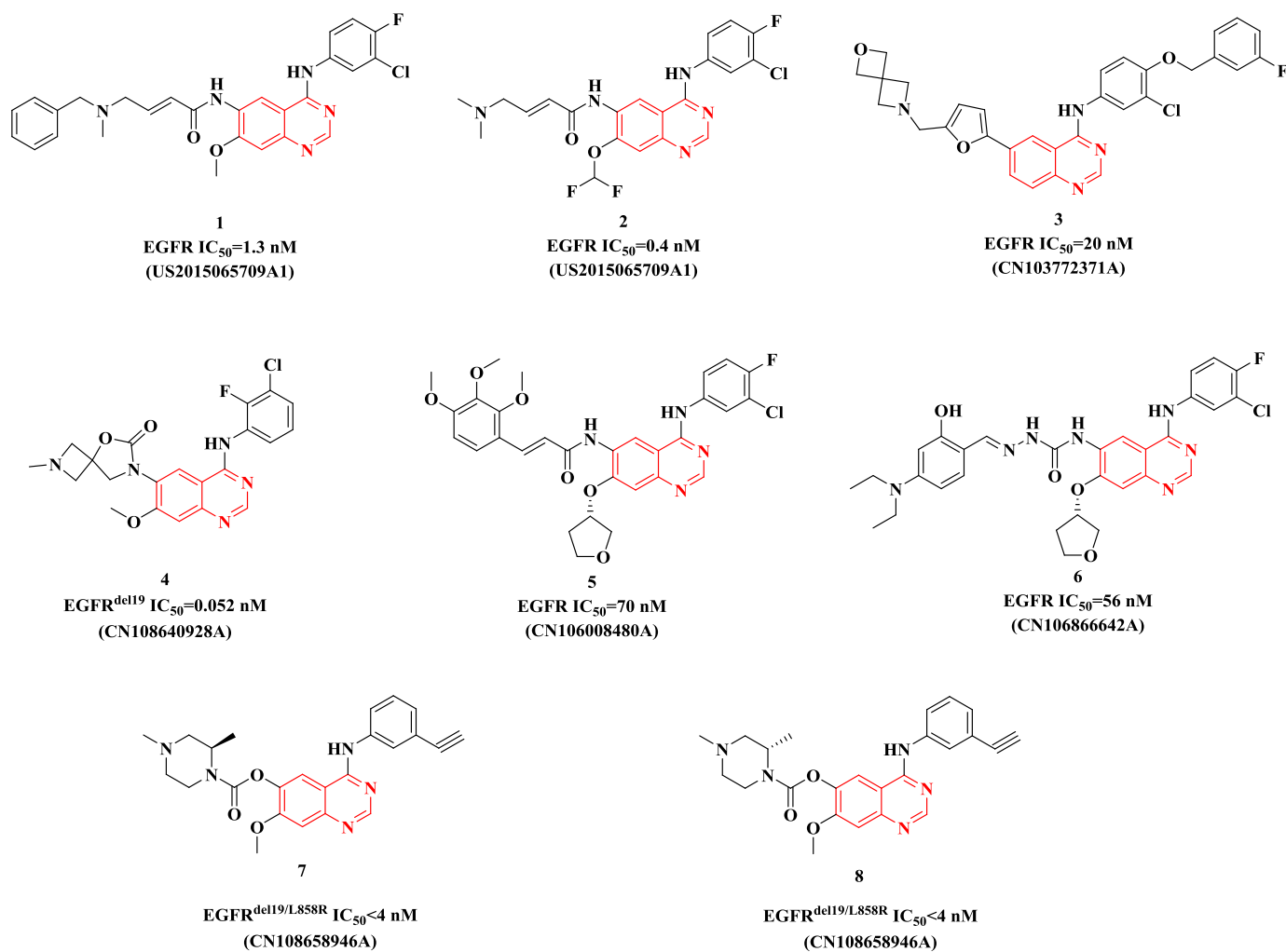
1
EGFR IC$_{50}$=1.3 nM
(US2015065709A1)

2
EGFR IC$_{50}$=0.4 nM
(US2015065709A1)

3
EGFR IC$_{50}$=20 nM
(CN103772371A)

4
EGFR^{del19} IC$_{50}$=0.052 nM
(CN108640928A)

5
EGFR IC$_{50}$=70 nM
(CN106008480A)

6
EGFR IC$_{50}$=56 nM
(CN106866642A)

7
EGFR$^{del19/L858R}$ IC$_{50}$<4 nM
(CN108658946A)

8
EGFR$^{del19/L858R}$ IC$_{50}$<4 nM
(CN108658946A)

Figure 1. Representative compounds with quinazoline structure.

(EGFR^{L858R}) and PC-9 (EGFR^{del19}) cells with IC$_{50}$ values less than 4 nM, while the inhibitory activity against Calu3 cells (expressing EGFR^{WT} gene) was weak, with IC$_{50}$ values of 143.4 and 171.2 nM, respectively. Consequently, they were expected to reduce the skin toxicity and gastrointestinal toxicity caused by the inhibition of wild-type EGFR. Apart from potent activity, they exhibited favorable brain barrier permeability, which was better than erlotinib [53].

3.2. Indole (benzopyrrole) derivatives as EGFR-TKIs

In order to solve the problem of drug resistance, it was necessary to develop inhibitors that selectively inhibit mutant EGFR to overcome the side effects such as dermatitis and diarrhea caused by the strong inhibitory effect of the first and second of generation inhibitors on wild-type EGFR in skin and intestine. This section summarized the compounds in the patent containing the core structure of indole and quinoline, which were hopefully used to treat NSCLC with EGFR mutation (Figure 2).

The patent **CN108250187A** innovatively introduced a carbonate structure on the nitrogen of indole based on AZD9291 and related compounds, finally designed and synthesized a series of compounds with a core ring of indole-1-carbonate. Among these compounds, representative compound **9** had an inhibitory effect on NSCLC cells NCI-H1975 (expressing EGFR$^{L858R/T790M}$ gene), with IC$_{50}$ values of 0.10 μM, which was equivalent to that of AZD9291 (IC$_{50}$ = 0.044 μM), and at the same time showed good selectivity and good safety in animals. In addition, it could significantly inhibit the phosphorylation of the EGFR$^{L858R/T790M}$ at the concentration of 10 nM and 100 nM, also had a potent effect on the phosphorylation of AKT and ERK in the downstream signaling pathway, the overall effect of which was analogous to AZD9291. Moreover, the in vivo evaluation of beagle dogs showed that it had good pharmacokinetic properties with t$_{1/2}$ of 7 h, plasma exposure and AUC of which were higher than AZD9291 as well [54]. In **WO2020002487A1**, a series of indole compounds developed by Hoffmann La Roche were selective isomeric inhibitors targeting contains T790M/L858R, T790M/L858R/C797S, L858R, and L858R/C797S mutant EGFR kinases. Representative compounds **10** and **11** showed excellent inhibitory ability of NCI-H1975 cells (EGFR$^{L858R/T790M}$) with IC$_{50}$ values of 1 nM and 3 nM, respectively. Moreover, they exhibited marked activity toward EGFR$^{L858R/T790M/C797S}$ kinase, with the IC$_{50}$ values of 5 and 4 nM, respectively, against mouse original B cell line BaF3 (EGFR$^{L858R/T790M/C797S}$) [55]. The patent **US2020102299A1** reported some EGFR$^{L858R/T790M}$ inhibitors
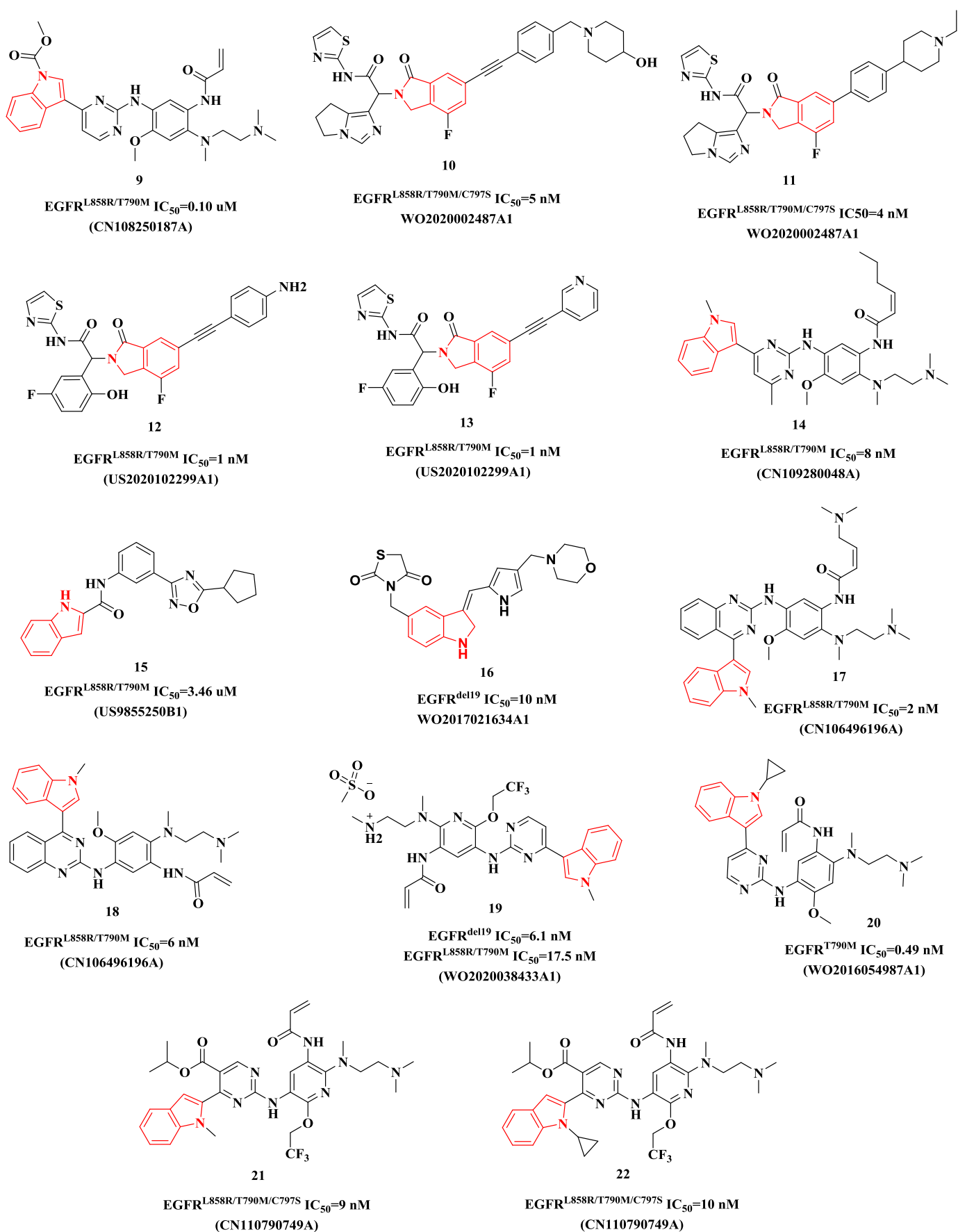
Figure 2. Representative compounds with indole structure.

structurally characterized by an isoindole acetylene skeleton, which were also developed from Hoffmann La Roche. Compounds **12** and **13** in the patent inhibited NCI-H1975 (EGFR$^{L858R/T790M}$) cells potently with IC$_{50}$ values of 1 and 1 nM. However, the kinase selectivity was not disclosed [56]. Indole compound **14** from **CN109280048A** showed excellent inhibitory ability of EGFR$^{L858R/T790M}$ double mutant kinase with IC$_{50}$ values of 8 nM. Based on the results of AO staining, a conclusion could be drawn that compound **14** inhibited NCI-H1975 (EGFR$^{L858R/T790M}$) cells proliferation and induced apoptosis at lower concentration [57]. Representative compound **15** from **US9855250B1** had the potential to treat NSCLC that was resistant to gefitinib. It induced the apoptosis of NCI-H1975 cells but no cytotoxicity on normal lung cells CCD-19Lu. And it showed IC$_{50}$ value of 3.46 μM against NCI-H1975. Nevertheless, it displayed IC$_{50}$ value more than 100 μM on CCD-19Lu [58]. The patent **WO2017021634A1** described the combination of compound **16** and erlotinib, aiming to provide a therapy proposal for patients with NSCLC who were resistant to EGFR tyrosine kinase. In the experiment of inhibiting the proliferation of HCC827 (EGFR^{del19}) cells, the median inhibitor concentration of the EGFR-TKI erlotinib for HCC827 cell survival was 10 nM. HCC827 cells resistant to erlotinib were obtained by exposure to erlotinib until the cell proliferation time was stable, which took approximately 2 months. Then, the median inhibitory concentration of erlotinib for cell survival of the resistant HCC827 cell was about 11.5 μM, which was about 1000 times higher than that as described above. The resistant cells were then exposed to compound **16** and an increasing dose of erlotinib in combination. It was worth noting that the use of compound **16** alone had no inhibitory effect on survival. In the combination, the median inhibitory concentration of erlotinib for the resistant cell line HCC827 returned to about 3.8 nM, which was close to the inhibitory power on the nonresistant cell line HCC827, indicating that it could restore sensitivity to EGFR tyrosine kinase inhibitors in NSCLC cells that were resistant to EGFR tyrosine kinase inhibitors. Moreover, their combined use could make HCC827 transplantation tumors completely resolved on the 19th day of oral administration. And when the treatment was stopped, the withdrawal time could last until the 30th day, which provided a research basis for later clinical trials [59]. Based on the mutant EGFR$^{L858R/T790M}$ kinases inhibition displayed IC$_{50}$ values ranged from 0.5 nM to 65 nM, most compounds from **CN106496196A**, such as compounds **17** and **18** were confirmed as EGFR$^{L858R/T790M}$ selective inhibitors. Moreover, compounds **17** and **18** exhibited potent inhibition on NCI-H1975 (EGFR$^{L858R/T790M}$) cells with IC$_{50}$ values of 2.0 and 6.0 nM, while the inhibitory activity on A549 (EGFR^{WT}) cells was weak, with IC$_{50}$ values more than 15 nM, which further confirmed their selectivity [60]. The patent **WO2020038433A1** reported some EGFR$^{L858R/T790M}$ inhibitors structurally featured by 2-aminopyridine-3-pyrimidine-1 H-indole scaffold, such as compound **19**. It had a potent anti-proliferative effect on a variety of mutant cells, with IC$_{50}$ values of 6.1, 3.1, and 17.5 nM, respectively, against on PC-9 (EGFR^{del19}) cells, NSCLC cell lines HCC827 (EGFR^{del19}) and NCI-H1975 (EGFR$^{L858R/T790M}$) cells, which were all stronger than AZD9291. The results of in vivo experiments in nude mice

showed that it had a marked inhibitory effect on the growth of HCC827 (EGFR^{del19}) and NCI-H1975 (EGFR$^{L858R/T790M}$) transplanted tumors, while its inhibitory effect on wild-type human squamous cell carcinoma A431 transplanted tumors was weak, indicating that it was a selective inhibitor [61]. Representative compound **20** from **WO2016054987A1** containing a 2-aniline pyrimidine scaffold, an indole group and an acrylamide group was reported to has IC$_{50}$ values of 0.49 nM on EGFR^{T790M} inhibition. More importantly, it exhibited excellent wild-type cell/mutant cell selectivity. And the pharmacokinetic parameters of compound **20** in beagle dogs were better than those of AZD9291, and the exposure dose was 6 times of that of AZD9291, the half-life of it was prolonged as well [62]. The compounds described in the patent **CN110790749A**, which were also derived from the structural modification of AZD9291, could significantly inhibit mutant EGFR. Representative compounds **21** and **22** showed effective anti-proliferative activity against BaF3 (EGFR$^{del19/T790M/C797S}$) cells with IC$_{50}$ values of 9 and 10 nM, respectively. They not only penetrated the blood–brain barrier and entered the brain tissue, but also showed excellent pharmacokinetic properties [63].

3.3. Benzimidazole and quinoline derivatives as EGFR-TKIs

Figure 3 listed the representative chemical structures of benzimidazole and quinoline derived from published patents.

Novartis had disclosed its invention compound **23** for the treatment of NSCLC with mutant EGFR, which was reported in patent **WO2016185333A1**. HCC827 (EGFR^{del19}) mice xenotransplantation model was very sensitive to compound **23**, and tumor regression could be achieved significantly at the lowest test day of 3 mg/kg, which was equivalent to the clinical-related dose of erlotinib (60 mg/kg). Moreover, it was well tolerated, and no weight loss was observed at the dose of 100 mg/kg, while erlotinib at 120 mg/kg showed significant weight loss. In NCI-H1975 (EGFR$^{L858R/T790M}$) mice and rats xenotransplantation models, significant tumor regression was achieved at the dose of ≥30 mg/kg. Importantly, compound **23** showed superior efficacy and significantly improved tolerance compared with the second-generation irreversible EGFR inhibitor afatinib. Therefore, compound **23** had the potential to provide therapy for patients with mutant EGFR resistance. It achieved significant anti-tumor activity in a mouse model of primary human lung cancer tissue (LU0387). Oral Compound **23** once a day for 18 days could cause tumor growth inhibition at a dose of 30 mg/kg. On the 18th day, the tumor regressed significantly (80%) when the dose was 100 mg/kg. It was well tolerated, and during the entire treatment period, there was little or no significant weight loss at any dose tested. In contrast, AZD9291 (25 mg/kg) was not well tolerated and showed severe weight loss. Finally, AZD9291 achieved only moderate tumor regression (26%) on day 18. In addition, in the study of recurrence time, after compound **23** treatment was stopped on the 21st day, the tumor stayed in almost complete regression for a week, and then showed slow tumor regrowth. On the contrary, after the AZD9291 treatment was stopped on the 21st day, tumor regrowth was immediately observed [64]. The purine derivatives developed by Boehringer-Ingelheim were published in patent
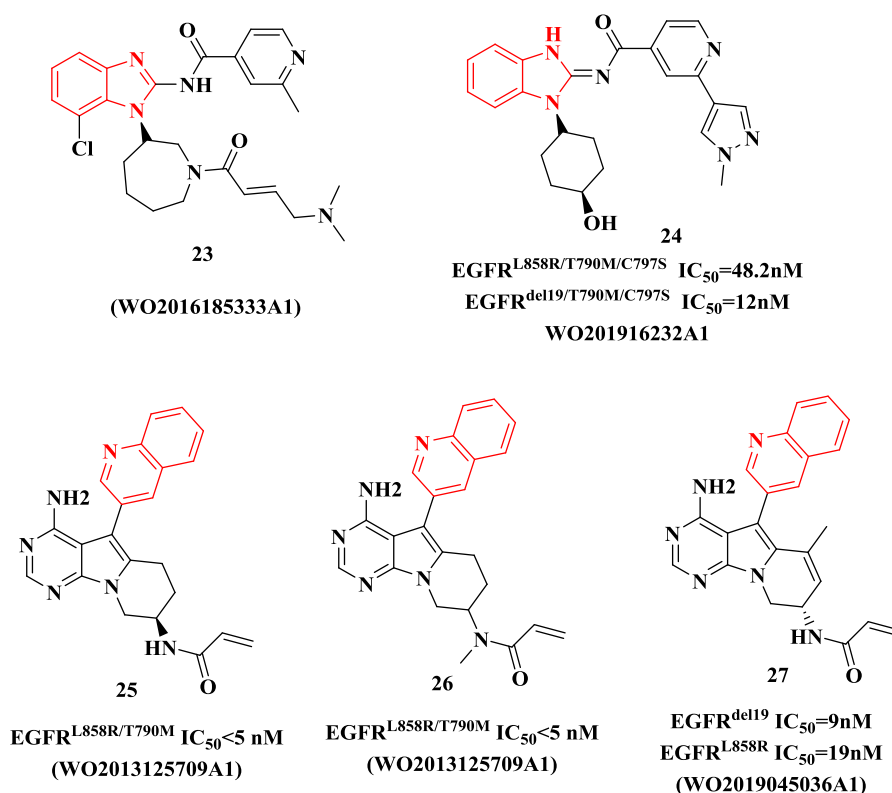
Figure 3. Representative compounds with benzimidazole quinoline structure.

WO201916232A1, and representative compound **24** was potent inhibitor of mutant EGFR, as demonstrated by its IC$_{50}$ values for EGFR$^{L858R/T790M/C797S}$ and EGFR$^{del19/T790M/C797S}$ of 48.2 and 12.0 nM, respectively, compared to control AZD9291 (1082.3 nM and 729.6 nM). In addition, compound **24** weakly inhibited wild-type EGFR with an IC$_{50}$ of 540 nM, which was lower than that of AZD9291 (26.7 nM), indicating that compound **24** had excellent selectivity [65].

A variety of quinoline derivatives were reported to inhibit mutant EGFR in patent **WO2013125709A1**. Among them, compounds **24** and **25** were highlighted as potent inhibitors for EGFR$^{L858R/T790M}$, EGFR$^{del19/T790M}$, EGFR^{L858R} and EGFR^{del19}, with IC$_{50}$ values below 0.5 nM. In NCI-H1975 (EGFR$^{L858R/T790M}$) and HCC827 (EGFR^{del19}) mutant cell lines, they also proved effective inhibition, and with a reduced efficacy against A431 (EGFR^{WT}) cells, reflecting a good potential for overcoming drug resistance [66]. In the patent **WO2019045036A1**, compound **26** with structure analogous to compound **24** demonstrated improved 的selective inhibition of exon 19 and exon 21 (L858R) mutant EGFR (IC$_{50}$ of 9.0 nM and 19.0 nM, respectively) in a murine interleukin-3 dependent pro-B cell lines BaF3 (EGFR$^{del19/T790M/C797S}$) compared to AZD9291 (IC$_{50}$ > 350 nM), and enhanced anti-tumor effect on nude mice transplanted with BaF3 tumor cells without weight loss or abnormal defecation [67].

3.4. Pyrimidine derivatives as EGFR-TKIs

The above-mentioned reversible inhibitors of EGFR with quinazoline or quinoline amine as the mother nucleus could not avoid the side effects caused by poor selectivity of wild-type cells. Compounds containing 2-anilinopyrimidine, such as

osimertinib (AZD9291), rociletinib (CO1686), and brigatinib (AP26113), have inhibitory activities against EGFR$^{L858R/T790M}$. Therefore, it is worth further developing compounds containing 2-anilinopyrimidine structure as selective inhibitors.

Figure 4 showed the representative chemical structures of EGFR inhibitors with aromatic aminopyrimidines derived from published patents. In the patent **WO2015117547A1**, representative compound **28** had a similar structure on CO1686, structurally featured by the phenylacrylamide attached to the 4-position of diaminopyrimidine, which formed an irreversible Michael addition reaction with protein cysteine when competing with ATP. Hence, compound **28** exhibited stronger inhibitory activity against EGFR$^{L858R/T790M}$ than CO1686 (IC$_{50}$ = 1.4 nM), with IC$_{50}$ value of 0.037 nM. Its antiproliferative activity against NCI-H1975 (EGFR$^{L858R/T790M}$) cells with IC$_{50}$ less than 10 nM was also better than that of CO1686 (IC$_{50}$ = 910 nM). In addition, at the 14th day, it possessed good efficacy in the NCI-H1975 xenograft study, and showed much better tumor growth inhibition with TGI value of 76% at a dose of 6 mg/kg compared with CO1686 [68]. Compounds **29** and **30** from **WO2015127873A1** with similar structures could selectively inhibit the double mutant EGFR$^{L858R/T790M}$ kinase with IC$_{50}$ values of 4 nM and 2 nM, respectively, while the inhibitory activity of EGFR^{WT} was weak. Furthermore, they showed IC$_{50}$ values of 37 nM and 31 nM, respectively, on cells NCI-H1975 (EGFR$^{L858R/T790M}$), having weak inhibitory activity against A431 (EGFR$^{L858R/T790M}$) cells, with obvious selective inhibitory activity. In order to identify their cytotoxicity, the toxicity test on mouse embryonic fibroblast cell lines was evaluated, and the results showed that these compounds had lower cytotoxicity [69]. **CN105968056A** disclosed a series of 2-aminopyrimidine compounds containing acrylamide groups, most of which had

28

EGFR$^{L858R/T790M}$ IC$_{50}$=0.037 nM
(WO2015117547A1)

29

EGFR$^{L858R/T790M}$ IC$_{50}$=4 nM
(WO2015127873A1)

30

EGFR$^{L858R/T790M}$ IC$_{50}$=2 nM
(WO2015127873A1)

31

EGFR^{T790M} IC$_{50}$=9 nM
(CN105968056A)

32

EGFR$^{L858R/T790M}$ IC$_{50}$=7nM
(CN105968056A)

33

H1975(EGFR$^{L858R/T790M}$)IC$_{50}$=0.1076 uM
WO2014210354A1

34

H1975(EGFR$^{L858R/T790M}$)IC$_{50}$=0.1443 uM
WO2014210354A1

35

H1975(EGFR$^{L858R/T790M}$)IC$_{50}$=0.1487 uM
WO2014210354A1

36

EGFR$^{L858R/T790M}$ Ki=0.702nM
WO2014081718A1

37

EGFR$^{L858R/T790M}$ Ki=0.81nM
WO2014081718A1

38

EGFR$^{del19/T790M/L718Q}$ IC$_{50}$=644 nM
US20170362204A1

39

EGFR^{T790M} IC$_{50}$=0.63 nM
(CN106187915A)

40

EGFR^{T790M} IC$_{50}$=0.26 nM
(CN106187915A)

41

EGFR^{del19},EGFR$^{L858R/T790M}$ GI$_{50}$=0.7 nM
ALK GI$_{50}$=67 nM
(CN106883213A)

42

EGFR$^{L858R/T790M/C797S}$ IC$_{50}$=0.218 nM
(WO2019015655A1)

43

EGFR$^{L858R/T790M/C797S}$ IC$_{50}$=0.212 nM
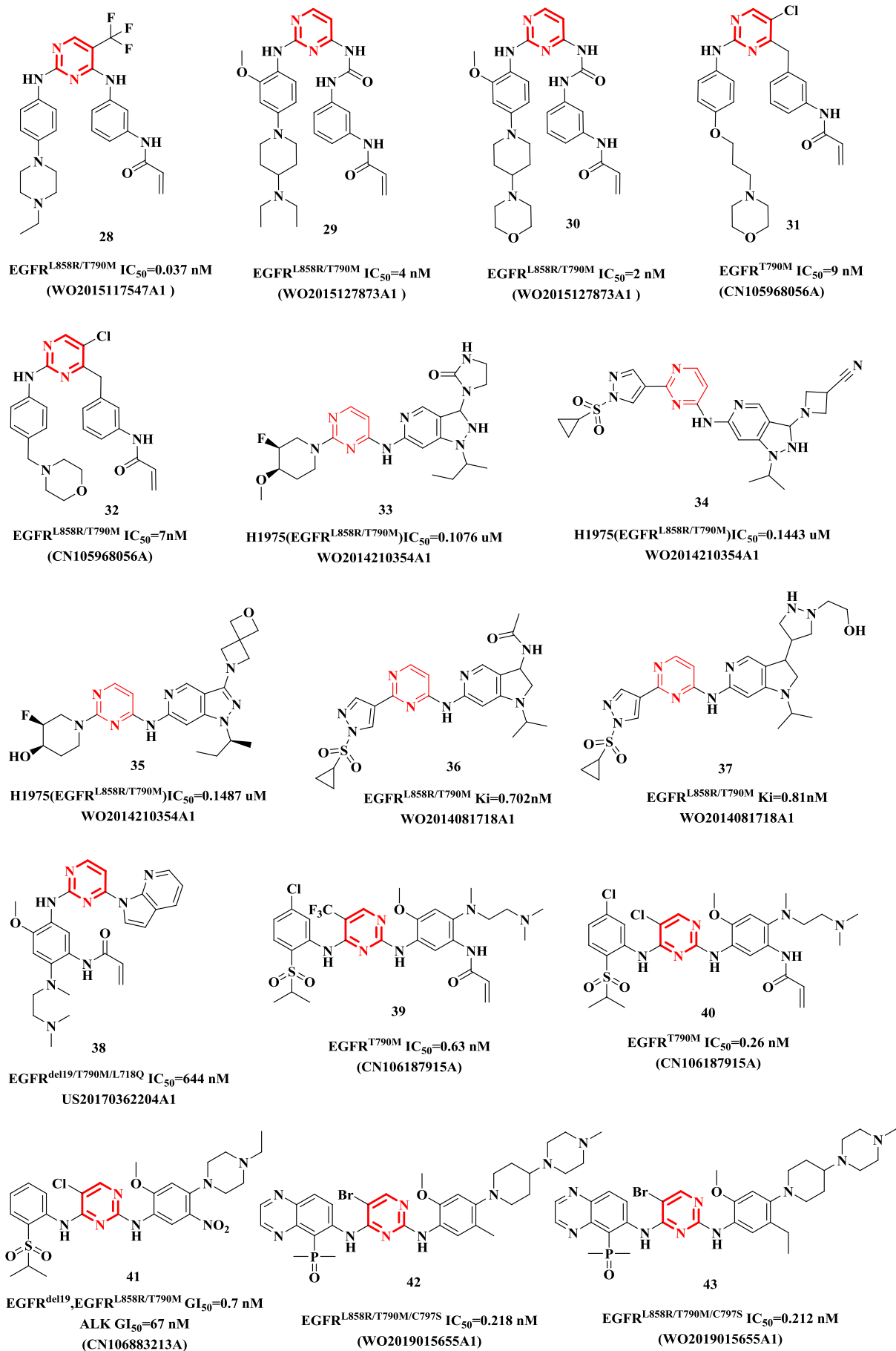(WO2019015655A1)

Figure 4. Representative compounds with pyrimidine structure.

strong inhibitory activity against EGFR^{T790M} kinase at the nano-molar level. Among them, the representative compounds **31** and **32** had IC$_{50}$ values of 9 nM and 7 nM, which were significantly better than gefitinib (IC$_{50}$ > 500 nM) and CO1686 (IC$_{50}$ = 8 nM). They also showed potent inhibition on cells NCI-H1975 (EGFR$^{L858R/T790M}$), with IC$_{50}$ values of 27 nM and 32 nM. In addition, they possessed inhibitory effects on MCF-7 cells and leukemia cells Ramos, which inspired us to further develop such compounds for the treatment of breast cancer and leukemia [70]. Patent **WO2014210354A1** published by Genetech covered 210 compounds containing 2-anilinopyrimidine structure as EGFR tyrosine kinase inhibitors. Three compounds with prominent activity were listed here, all of which showed strong inhibitory proliferative potency against NCI-H1975 (EGFR$^{L858R/T790M}$) cells. The EC50 values of compounds **33, 34** and **35** for the antiproliferative of NCI-H1975 cells were 0.1076, 0.1443 and 0.1487 μM, respectively. Meanwhile, their EC50 values for the EGFR phosphorylation inhibitory in NCI-H1975 cells were 0.0144, 0.0289 and 0.0128 μM, respectively [71]. The patent **WO2014081718A1**, also from Genetech, reported the synthesis and bioactivity test of 707 2-anilinopyrimidine derivatives. Among them, the biochemical activities of representative compounds **36** and **37** to EGFR$^{T790M/L858R}$ were reflected in Ki values of 0.702 and 0.81 nM, respectively. In addition, they had strong antiproliferative activity to NCI-H1975 (EGFR$^{L858R/T790M}$) cells with IC$_{50}$ values of 0.44 and 0.209 μM, respectively [72]. Pyrimidine compound **38** from **US20170362204A1** reported by Dana-Farber Cancer Institute exhibited potent inhibition of EGFR$^{del19/T790M/L718Q}$, with IC$_{50}$ values of 644 nM, which was stronger than that of WZ4002 (2005.5 nM) and AZD9291 (576 nM). It had an IC$_{50}$ value of 323 nM against wild-type EGFR, less potent than WZ4002 (100 nM) and AZD9291 (23.0 nM), indicating that compound **38** was more selective [73].

Compounds disclosed in **CN106187915A** were structurally analogous to the positive control drug ceritinib (LDK378) which was an anaplastic lymphoma kinase (ALK)-positive inhibitor primarily used for the treatment of metastatic NSCLC. It was worth mentioning that the rearrangement of echinoderm microtubule-associated protein (EML4) gene and ALK gene were discovered in 2007 in lung cancer patients. EML4-ALK gene rearrangement mainly occurred in non-small cell lung cancer, so the development of ALK inhibitors was of positive significance for the treatment of non-small cell lung cancer. Representative compounds **39** and **40** exhibited dual inhibition of EGFR and ALK. compound **39** of them showed IC$_{50}$ values of 0.63 nM and 3.2 nM, respectively, against EGFR^{T790M} and ALK. Substitution of the trifluoromethyl group on the 5-position of the pyrimidine ring in compound **39** by chlorine atom led to compound **40**, which showed higher inhibition than compound **39** with IC$_{50}$ values of 0.26 nM and 2.1 nM, respectively, against EGFR^{T790M} and ALK. The results of in vitro cell antiproliferation experiments on NCI-H1975 and human lymphoma cell lines Karpas299 with high expression of ALK gene showed that they had potent inhibitory effects, which were better than compound ceritinib [74]. Another compound **41** as a dual inhibitor of mutant EGFR and ALK from **CN106883213A** showed potent inhibitory activity against several cell lines. The effects of inhibitors on several cell signaling pathways were evaluated, and the results showed that it had almost no effect on the phosphorylation of

EGFR protein of A549 (EGFR^{WT}) cells. As for PC-9 (EGFR^{del19}) cells, NCI-H1975 (EGFR$^{L858R/T790M}$) cells and mouse BaF3-TEL-ALK (expressing ALK gene) cells, it could obviously inhibit the phosphorylation of EGFR protein at very small concentrations, with GI$_{50}$ values of 0.7 nM, 67 nM, and below 0.3 nM. Similarly, it could induce apoptosis of PC-9, and NCI-H1975, while blocking the cells in G0-G1 phase in a concentration-dependent manner. However, it was unable to induce apoptosis of A549 (EGFR^{WT}) cell lines and had little effect on cell cycle, therefore affording high double mutant EGFR selectivity and inhibited ALK kinase. In the mouse model experiments of PC-9 cells and NCI-H1975 cells, it could completely inhibit the tumor at low dose (25 mg/kg) in 8 days, and had almost no effect on the weight of mice [75]. Pyrimidine compounds containing aryl phosphorus oxides disclosed in **WO2019015655A1** showed excellent performance in the anti-proliferation and anti-phosphorylation activity of BaF3 (EGFR$^{del19/T790M/C797S}$) triple mutant cells. Representative compounds **42** and **43** inhibited EGFR^{WT}, EGFR$^{del19/T790M/C797S}$ and EGFR$^{L858R/T790M/C797S}$ with IC$_{50}$ values of 7.92, 0.218, and 0.16 nM, as well as 5.12, 0.212, and 0.26 nM, respectively, which suggested they were potent and selective triple mutant EGFR inhibitors. Moreover, they displayed good stability in EGFR BaF3 xenograft nude mice liver microsomes with t$_{1/2}$ of 10 and 20.5 h, respectively, pharmacokinetic effects of which was better than that of britigatinib [76].

3.5. Purine and pyrazolo[5,6-*d*]pyrimidine derivatives as EGFR-TKIs

This chapter summarized the derivatives with purine and pyrazolo[5,6-*d*]pyrimidine core structures as promising EGFR inhibitors. The structures of representative compounds in these patents were listed in Figure 5.

The patent **WO2015075598A1** covered the preparation of a series of 2,6-substituted purine derivatives developed by Pfizer, and the evaluation for cells under different mutation conditions inhibitory activity of all derivatives. Among them, compounds **44** and **45** possessed significant inhibitory effects on NSCLC cell lines, specifically the IC$_{50}$ values for NCI-H1975 (EGFR$^{L858R/T790M}$) cells, NCI-H3255 (EGFR^{L858R}) cells and PC-9 (EGFR^{del19}) cells range from 1 nM to 9 nM by measuring the phosphorylation degree of EGFR on tyrosine in cells, and poor inhibitory effects (IC$_{50}$ > 150 nM) on wild-type cells, proving their excellent selectivity [76]. The patent **WO2015075598** mentioned that compound **44** (PF-06747775) was being used as a single agent for NSCLC patients with advanced EGFR mutations (del19 or L858R) in phase I/II clinical trials [77]. **CN105884777A** contained compounds **46** and **47** with 6-substituted aminopurine skeleton acting EGFR sensitive mutant kinase EGFR^{L858R} and EGFR^{del19}, inhibition effect of which reached nanomolar level, with IC$_{50}$ values of 84 and 82 nM against EGFR^{L858R}, and with IC$_{50}$ values of 96 and 99 nM against EGFR^{del19}. On the other hand, they displayed weak inhibition against EGFR^{WT} kinase [78]. Representative compound **48** from **CN107892691A** containing a 2,8,9-trisubstituted-9 H-purine moiety was reported to has excellent inhibition against mutant EGFR. Specifically, it inhibited EGFR^{L858R} up to 100% at a concentration of 10 nM, which was stronger than the 76% inhibition of AZD9291. At a dose of 5.0 mg/kg, administered by gavage for 14 days, it significantly inhibited
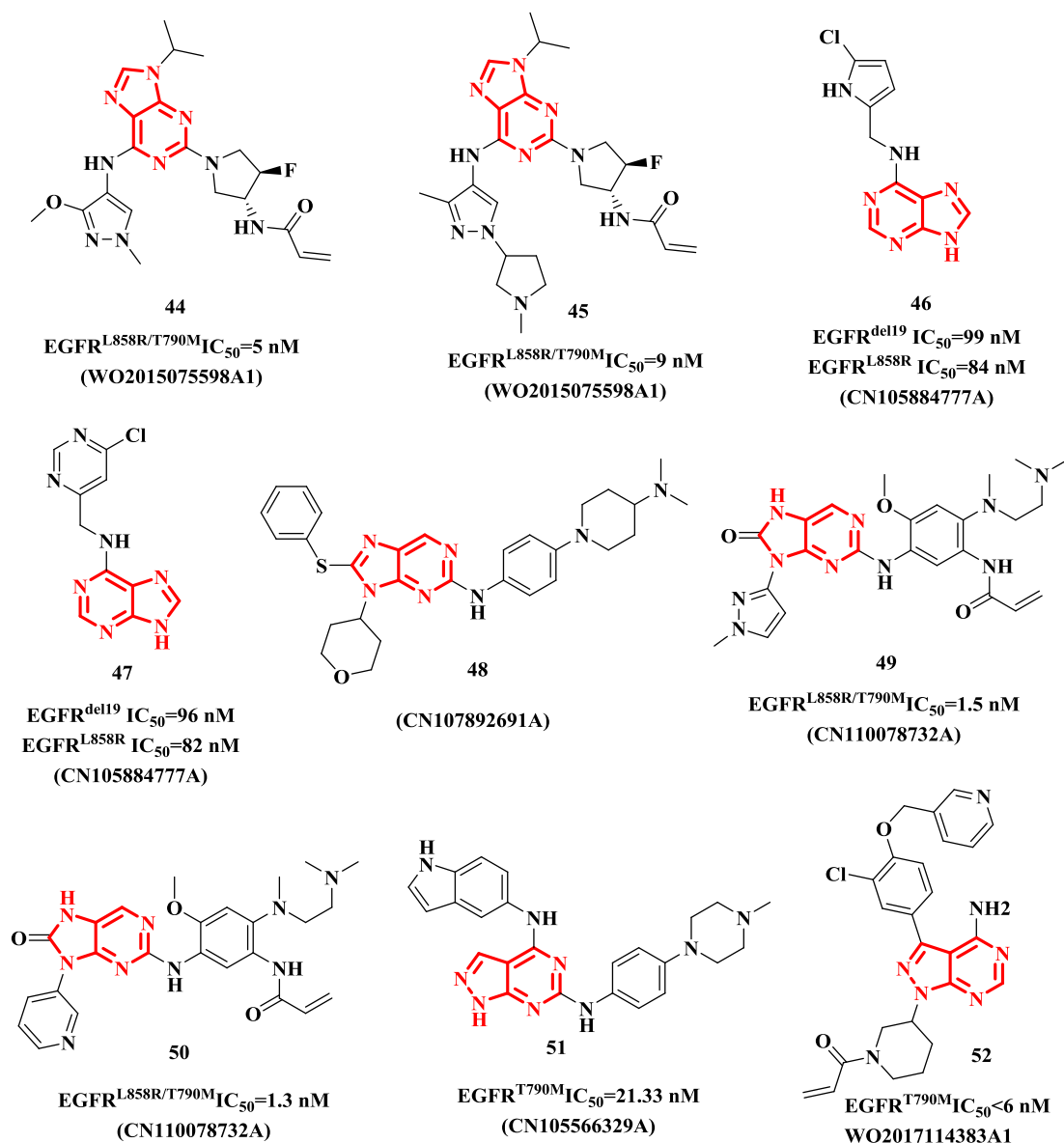
Figure 5. Representative compounds with purine and pyrazolo[5,6-d]pyrimidine structure.

the growth of HCC827 (EGFR^{del19}) xenograft tumors. It was noteworthy that the compound had a relatively small ClogP values based on the 9-position of the purine ring attached to the 4-tetrahydropyranyl group. At the same concentration, it presented better drug-forming properties compared to AZD9291 [79]. Patent **CN110078732A** provided 36 compounds that could be used against overexpression of single mutant EGFR^{T790M} and double mutant EGFR$^{L858R/T790M}$, represented by compound **49** (IC$_{50}$ = 2.5 and 1.5 nM) and **50** (IC$_{50}$ = 3.4 and 1.3 nM) [80].

The patent **CN105566329A** identified compound **51** containing the core structure of pyrazolo[5,6-d]pyrimidine as a selective inhibitor of EGFR^{T790M}. The in vitro kinase activity screening test confirmed that it had a strong EGFR^{T790M} inhibitory activity, which showed an IC$_{50}$ value of 21.33 nM. Experiments at the cell level also proved that it could effectively inhibit the phosphorylation level of EGFR and its downstream signals p-Akt and p-Erk [81]. The patent

WO2017114383A1 reported the synthesis of 54 compounds that demonstrated a wide range of mutant and wild EGFR inhibitory activity. Numerous compounds exhibited EGFR inhibition with inhibition activity reached nanomolar level. Among them, the representative compound **52** specifically showed that the IC$_{50}$ values of anti-proliferation against NCI-H1975 (EGFR$^{L858R/T790M}$), PC-9 (EGFR^{del19}) and A431 (EGFR^{WT}) cells were less than 6 nM. In an experimental study of the effect of the inhibitor on apoptosis, it was found that it could not induce apoptosis in A549 (EGFR^{WT}) cells for 72 hours. However, it caused apoptosis in many mutant cells such as NCI-H1975 cells, PC-9 cells, HCC827 (EGFR^{del19}) cells, and NCI-H3255 (EGFR^{L858R}) cells, as evidenced by a significant shearing of the DNA repair enzyme PARP (poly ADP-ribose polymerase) at a concentration of 0.03 μM for 48 hours after administration. Furthermore, it significantly inhibited tumor growth in PC-9 cells mouse tumor model and NCI-H1975 mouse tumor
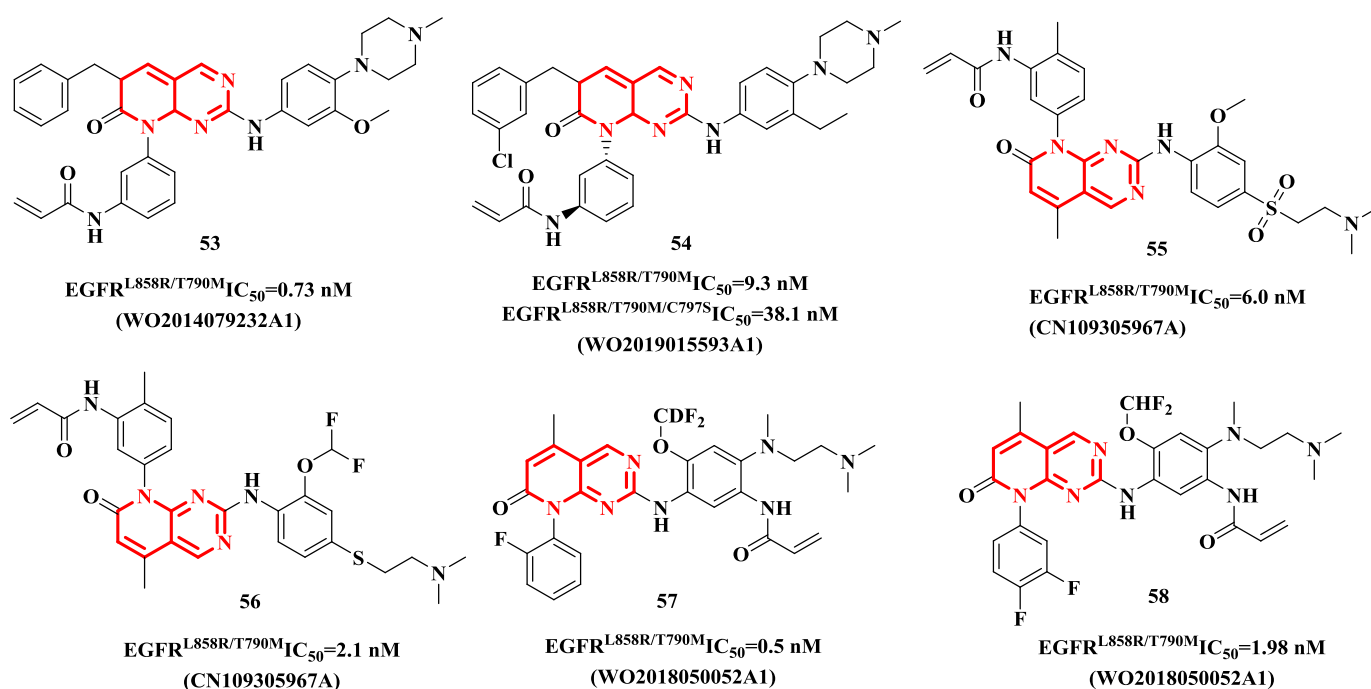
Figure 6. Representative compounds with pyrido[2,3-*d*]pyrimidine and structure.

model with up to 50% inhibition and almost no effect on body weight, suggesting that it could be deeply optimized for development into selective anti-NSCLC drugs [82].

3.6. Pyrido[2,3-*d*]pyrimidine derivatives as EGFR-TKIs

In recent years, some published patents provided selective inhibitors based on the pyridopyrimidine system. This part summarized these compounds, and some representative compounds which were showed in Figure 6 also exhibited good inhibitory activity against mutant EGFR.

A variety of 7-oxopyrido[2,3-*d*]pyrimidine derivatives were reported in **WO2014079232A1** to inhibit EGFR with single mutation and double mutation. These compounds all showed excellent performance in vitro EGFR protein kinase inhibitory activity test. Among them, compound **53** afforded the strongest resistance to EGFR with T790M, L858R, L861Q and L858R/T790M mutations, with IC_{50} values of 0.98, 0.52, 0.42, and 0.73 nM. In addition, it was evaluated to inhibit cell proliferation of NCI-H1975 ($EGFR^{L858R/T790M}$) and HCC827 ($EGFR^{del19}$). These effects were due to the existence of the compounds that formed an irreversible Michael addition reaction with the protein cysteine site, indicating that the acrylamide structure was a necessary structure for the compound to maintain activity [83]. **WO2019015593A1** contained numerous compounds modified by compound **53**. Representative compound **54** exhibited IC_{50} values of 3.8, 9.3, and 38.1 nM against on $EGFR^{WT}$, $EGFR^{L858R/T790M}$, $EGFR^{L858R/T790M/C797S}$. Furthermore, it was demonstrated that compound **54** significantly inhibited the proliferation of BaF3 ($EGFR^{L858R/T790M/C797S}$) cells, and the rate of inhibition was positively correlated with the concentration [84]. Patent **CN109305967A** described a series of novel pyrido[2,3-*d*]pyrimidin-7-ketone compounds that had much

better activity and selectivity to double mutant EGFR kinase than AZD9291. Compound **55** and compound **56** of them maintained strong $EGFR^{L858R/T790M}$ inhibition with IC_{50} values of 6.0 and 2.1 nM, while having IC_{50} values more than 1000 nM against on $EGFR^{WT}$ [85]. Representative compounds **57** and **58** in **WO2018050052A1** demonstrated potent inhibition of $EGFR^{L858R/T790M}$, IC_{50} values were reported to be 0.50 and 1.98 nM. Furthermore, they were proved to be selective inhibitors, selective inhibitory activity data of compound **57** was up to 60 times of AZD9291 [86].

4. Conclusion

In conclusion, selective mutant EGFR inhibitors have recently received great attention in the field of oncology drugs discovery, especially against NSCLC. Although some FDA-approved EGFR inhibitors (e.g., afatinib, dacomitinib, AZD9291, and olmutinib) have shown effective clinical effects in the treatment of non-small cell lung cancer (NSCLC), clinical resistance mutations are the main obstacle to the wide application of EGFR inhibitors problem. Therefore, researchers remain enthusiastic about the development of new EGFR inhibitors with low toxicity and high safety, and numerous chemical structures have been reported in recent patents and papers. This review summarizes the chemical structure of EGFR inhibitors with anti-tumor activity discovered in the patents from 2014-present, which provides motivation for the development of efficient, novel, and selective EGFR inhibitors and their application prospects in NSCLC treatment.

5. Expert opinion

In view of the high incidence and mortality of non-small cell lung cancer, traditional treatment methods are difficult to

achieve satisfactory therapeutic effects due to poor selectivity and large side effects. EGFR is overexpressed and activated in a variety of malignant tumors such as breast cancer, lung cancer, ovarian cancer, cervical cancer, esophageal cancer, prostate cancer, liver cancer, colon cancer, gastric cancer, etc [87]. EGFR can accelerate the reproduction of tumor cells, promote tumor angiogenesis, accelerate tumor metastasis, and hinder tumor apoptosis. In this context, the development of highly effective targeting EGFR drugs to treat NSCLC has become a research hotspot. There are two main types of drugs that target EGFR: one is small molecule tyrosine kinase inhibitors (TKIs) that act on the intracellular region of the receptor, and the other is monoclonal antibodies (Mab) that act on the extracellular region of the receptor. This review mainly describes TKIs [88].

In non-small cell lung cancer (NSCLC), about 50% of patients presented EGFR mutations, which were caused by the deletion, mutation, and rearrangement of EGFR gene. The small molecule inhibitors gefitinib and erlotinib, which could target the most common activating mutation of EGFR, L858R point mutation, and exon 19 deletion, had been approved by the FDA for the treatment of patients with advanced NSCLC. Compared with traditional chemotherapy, they did not produce side effects such as bone marrow suppression and neurotoxicity. However, after 1 year of use, the patient appeared to be resistant to the drug. The T790M mutation of the EGFR gene was the main reason for resistance to these drugs, and the replacement of threonine residues by methionine residues with larger side chains created a steric hindrance effect that increased the affinity of ATP for EGFR, which hindered the binding of the inhibitor to the EGFR tyrosine kinase, ultimately leading to loss of inhibitor activity [89]. The advantages of second-generation inhibitors such as afatinib and dacomitinib over the first-generation inhibitors were that they had enhanced recognition of EGFR, which could distinguish tumor cells from normal cells, thereby reducing side effect [90]. However, these molecules had poor selectivity for EGFR^{T790M} mutants, because they showed strong inhibitory effects on wild-type EGFR in the skin and intestines, causing side effects such as dermatitis and diarrhea, which reduced the quality of life of patients receiving treatment. In addition, under its maximum tolerated dose (MTD), the drug could not reach its effective concentration in the body. As a result, it was ineffective for most drug-resistant patients [91]. This prompted researchers to study EGFR inhibitors that were more selective between wild-type EGFR and T790M mutant. The third-generation mutation-selective EGFR inhibitor osimertinib (AZD9291) developed by AstraZeneeca had a good therapeutic effect on NSCLC patients with EGFR-TKI resistance and T790M mutation. The third-generation inhibitors containing aminopyrimidine groups can form a covalent bond with Cys797 residues in the EGFR tyrosine kinase ATP-binding site, blocking the signal pathway of EGFR^{T790M} mutant cells and inhibit cell growth [92]. However, a new C797S integration was found in EGFR exon 20 of NSCLC patients treated with third-generation irreversible EGFR inhibitors, indicating that drug resistance has become the biggest challenge.

In response to these problems of drug resistance and poor selectivity, it is of great significance to develop novel selective inhibitors of EGFR mutants with higher activity, better selectivity and lower toxicity. In addition, the combination of drugs can enhance the curative effect to a certain extent, reduce drug dosages and weaken toxic side effects, which is a direction worthy of further exploration. Reversible or irreversible EGFR inhibitors based on quinazoline inevitably produce toxic side effects due to their poor selectivity to wild-type cells. Some of the novel structures reported in this article, such as indole, pyrimidine, and heterocyclic pyrimidine, have good selectivity and strong inhibition of mutant EGFR activity. Particularly, the third-generation inhibitors containing Michael receptor fragments such as benzyl ether, benzylamine, or arylamide can covalently bond to cysteine residues (Cys797) located in the ATP-binding pocket and produce irreversible inhibition, so they have high kinase inhibitory activity against the T790M mutant EGFR. Although these drugs have great potential, under the current state of the art, their development is mainly in the preclinical stage. But it is undeniable that the compounds in these reported patents are instructive for further exploration of new and effective EGFR inhibitors.

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