Review

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Research progress in quinazoline derivatives as multi-target tyrosine kinase inhibitors

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Abstract: Receptor tyrosine kinases (RTKs), such as epidermal growth factor receptor (EGFR), are involved in multiple human tumors. Therefore, RTKs are attractive targets for various antitumor strategies. Two classes of tyrosine kinase antagonists were applied in the clinic for monoclonal antibodies and small-molecule tyrosine kinase inhibitors. A well-studied class of small-molecule inhibitors is represented by 4-anilinoquinazolines, exemplified by gefitinib and erlotinib as mono-targeted EGFR inhibitors, which were approved for the treatment of non-small-cell lung cancer. Mono-target drugs may result in drug resistance and the innovation of multi-target drugs has grown up to be an active field. Recent advances in research on antitumor bioactivity of 4-anilino(or phenoxy)quinazoline derivatives with multiple targets are reviewed in this paper. At the same time, synthetic methods of quinazolines were introduced from the point of building the ring skeleton and based on the types of reaction.

Keywords: antitumor; multiple targets; quinazoline; receptor tyrosine kinases; synthesis.

Introduction

Quinazolines (Figure 1) show extensive biological activities [1–6]. Their synthetic methods are important topics for pharmaceutical research. The 4(3*H*)-quinazolinone core plays a significant role in the most commonly applied synthetic methods. Microwave-assisted synthetic methods, acid-catalyzed synthetic methods and metal-catalyzed synthetic methods are also applied in their synthesis. Quinazoline derivatives are important antitumor drugs as small-molecule inhibitors especially in the area of receptor tyrosine kinase (RTK) inhibitors. The downstream signaling pathways of RTKs are closely related to the occurrence of the tumor, which can induce several oncogenic effects including enhancing cell proliferation, aberrant differentiation, malignant transformation and migration in solid tumor cells. Inhibiting the activity of the receptors could block the downstream signaling pathways of growth factors and effectively inhibit the growth of tumors [7]. Cancer is a disease usually accompanied by a disorder of multiple signaling pathways. Mono-target drugs may result in drug resistance [8], and the innovation of multi-target drugs has grown up to be an important field. Developing multi-target RTK inhibitors acting on multiple signal pathways could regulate multiple signaling pathways at different levels resulting in better antineoplastic activity.

The structure-activity relationship of quinazolines (Figure 1) can be summarized as follows:

1. Modifications in the A and C rings affect the ability of the compounds to inhibit epidermal growth factor receptor (EGFR)-tyrosine kinases. Both of the nitrogen atoms of quinazoline are essential for inhibitory activity. The phenyl ring with a small lipophilic substituent such as a chloro, bromo or trifluoromethyl group is important as it occupies the lipophilic pocket. The character of the linking group between the quinazoline ring and phenyl side chain makes a big difference in the inhibitory activity. Replacing the nitrogen linker by an oxygen or sulfur atom may result in the reduction of EGFR inhibitory activity. On the other hand, it may increase vascular endothelial growth factor receptor (VEGFR) inhibitory activity. Derivatives of the urea or thiourea group linked to the phenyl side chain are more potent.
2. Modifications in the B ring affect the inhibitory activity. The presence of a polar group at the 6- or 7-position of the quinazoline ring is beneficial. The absence

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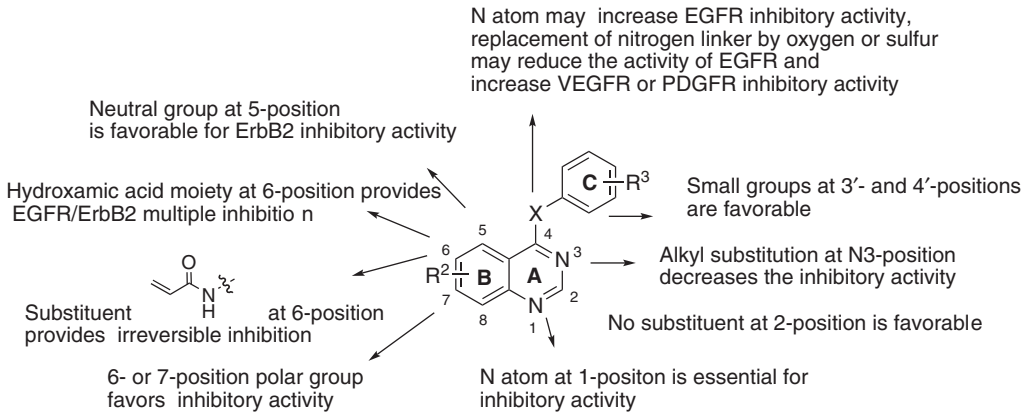


Figure 1 Structure-activity relationship of quinazolines.

of a substituent at the 2- or 3-position of quinazoline favors the inhibitory activity. Otherwise, the presence of a propylene amide or acetylene group at the 6-position of quinazoline can result in EGFR/ErbB2 irreversible inhibition. Introducing the hydroxamic acid moiety at the 6-position of quinazoline can result in EGFR/ErbB2 multiple kinase inhibition. The presence of a large neutral substituent at the 5-position can enhance ErbB2 inhibitory activity.

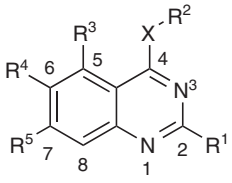
Quinazoline derivatives as multi-target EGFR family kinase inhibitors

EGFR is overexpressed in the majority of non-small-cell lung cancers and its expression is inversely related to survival outcome. EGFR and ErbB2 are two important validated target molecules in cancer treatment. Several single-target EGFR 4-aminoquinazoline compounds are applied in the clinic. Drug resistance is inevitable among the first generation [9]. Research on 4-anilinoquinazoline mono-target drugs shows that introducing a bulky lipophilic group at the 4-position of quinazoline can improve multiple inhibitory activities of the EGFR family, hence the occurrence of drug resistance can be reduced. Based on this finding, lapatinib (**1a**) in Table 1 was developed as a new kind of selective EGFR/ErbB2 dual inhibitor with an inhibitory concentration (IC_{50}) value of 10.2 nM and 9.8 nM, respectively. The downstream cell proliferation signal is blocked by the reversible combination of EGFR/ErbB2 and adenosine triphosphate (ATP) active sites [10]. Our research group [11] also designed and synthesized several highly effective compounds, some of which are active in the micromolar range of IC_{50} values against MCF-7 and A-549 cells. Propylene amide or acetylene groups were introduced at the 6-position of quinazoline to afford a series of EGFR/ErbB2 irreversible inhibitors **1b–e** with the IC_{50} at the nanomolar level for EGFR kinase and HER2 kinase. Structure-activity and molecular modeling studies suggested that positioning of the acrylamide moiety at the 6-position can effectively reduce the resistance to the first generation of EGFR inhibitors [12–15]. A neutral hydroxyacylamino moiety was introduced into the anilinoquinazoline to furnish a RTK inhibitor **1f**. Its IC_{50} values for the EGFR and ErbB2 kinases are around 2 nM [16]. Compound AZD8931 (**1g**) is a reversible inhibitor of phosphorylation of EGFR, HER2 and HER3 and demonstrates potent *in vitro* inhibition against isolated HER2 and EGFR tyrosine kinases with the respective IC_{50} values of 14 nM and 12 nM against HER2 and EGFR [17]. Compound **1h** with an oxazine ring shows significant cytotoxic activities with the IC_{50} values of 3 nM and 250 nM against HER2 and EGFR, respectively. It shows better inhibitory activities against several cell lines compared to gefitinib and erlotinib, with extensive antiproliferative activities [18].

Quinazoline derivatives as multi-target EGFR and VEGFR family kinase inhibitors

VEGFR-2 plays a major role in tumor angiogenesis, which is regarded as the most important molecular target for inhibiting angiogenesis [19]. The drug targeting the EGFR and VEGFR-2 pathways can inhibit both tumor cells and tumor angiogenesis, hence a better therapeutic effect can be achieved. Vandetanib (ZD6474, **1i**) is a potent tyrosine kinase inhibitor targeting the VEGFR tyrosine kinase (IC_{50} = 40 nM) and the EGFR tyrosine kinase (IC_{50} = 500 nM) [20]. Compound **1j** has two individual reactive centers and was designed to target a cysteine residue located in the

Table 1 Quinazoline derivatives as multi-target tyrosine kinase inhibitors.



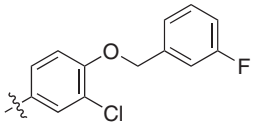
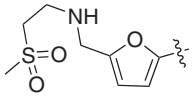
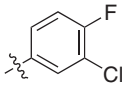
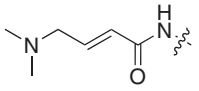
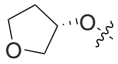
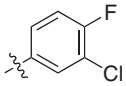
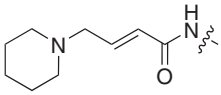
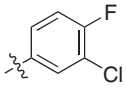
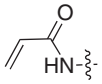
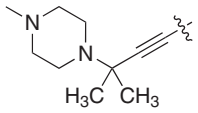
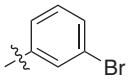
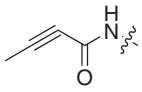
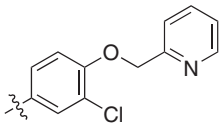
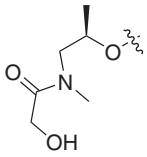
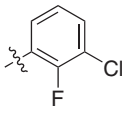
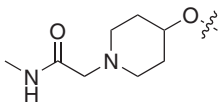
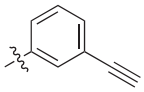
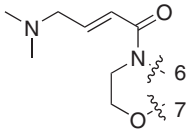
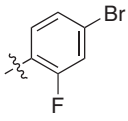
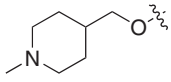
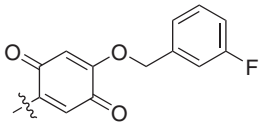
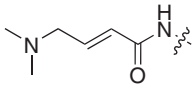
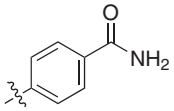
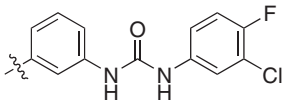
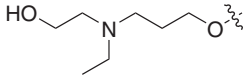
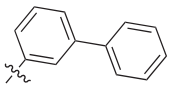
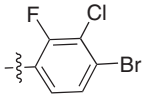
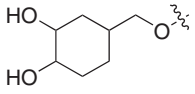
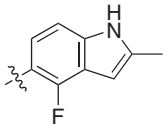
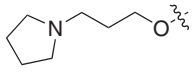
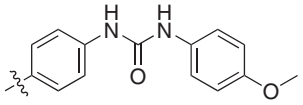
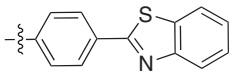
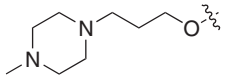
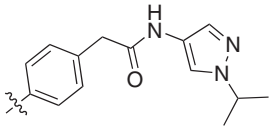
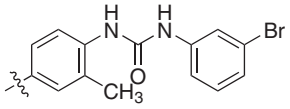
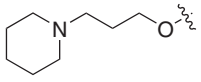
Compd.	Target	X	R^1	R^2	R^3	R^4	R^5
1a	EGFR/ErbB2	NH	H		–		–
1b	EGFR/ErbB2	NH	H		–		
1c	EGFR/ErbB2	NH	H		–		
1d	EGFR/ErbB2	NH	H		–		
1e	EGFR/ErbB2	NH	H		–		–
1f	EGFR/ErbB2	NH	H			–	–
1g	EGFR/ErbB2/ ErbB3	NH	H		–		
1h	EGFR/ErbB2	NH	H		–		
1i	EGFR/VEGFR	NH	H		–		
1j	EGFR/VEGFR	NH	H		–		
1k	EGFR/VEGFR	NH	Cl		–		
1l	EGFR/VEGFR	NH	H		–	–	

Table 1 (continued)

Compd.	Target	X	R^1	R^2	R^3	R^4	R^5
1m	EGFR/VEGFR	NH	H		–		
1n	EGFR/VEGFR	NH	H		–		
1o	VEGFR/ PDGFR	O	H		–		
1p	VEGFR/ PDGFR	O	H		–		
1q	VEGFR/ PDGFR	O	H		–		
1r	VEGFR/ PDGFR	O	H		–		
1s	VEGFR/ PDGFR	O	H		–		

ATP binding pocket of both EGFR and VEGFR-2. The IC_{50} values against them are 4.1 nM and 113.4 nM, respectively [21]. The hydrogen bond donor lies at the *para* position of the aniline moiety of compound **1k** and plays an important role in binding with amino acids of EGFR and VEGFR-2 [22].

In 2013, Zhang and co-workers [23] designed a hybrid approach that combines two privileged pharmacophores, namely 4-anilinoquinazoline and unsymmetrical diarylurea, to successfully deliver a novel series of multi-kinase inhibitors. Compound **1l** exhibits profound activity against BRAF, BRAF V600E, VEGFR-2 and EGFR. The IC_{50} values against EGFR and VEGFR-2 are 165 nM and 95 nM, respectively. Compound **1m** has a 1,3-dioxolane moiety fused to the quinazoline portion and a biphenylamino substituent as the aniline portion, which provide a significant anti-angiogenic effect in both *in vitro* and *in vivo* assays even at noncytotoxic concentrations [24]. Shi and co-workers [25] synthesized a series of EGFR/VEGFR-2 tyrosine kinase inhibitors. The inhibitory activities of the optimized compound **1n** against EGFR and VEGFR-2 *in vitro* are 15 nM and 32 nM, respectively, which is better than that of the reference compound vandetanib. These findings may provide new insights for seeking new multi-targeting anticancer candidate compounds.

Quinazoline derivatives as multi-target VEGFR and PDGFR family inhibitors

VEGFR and platelet-derived growth factor receptor (PDGFR) mediate two important signaling pathways in tumor angiogenesis. Because of the compensation between signaling pathways, inhibition of either one of the signaling pathways can result in enhancing of the other signaling pathways, thus triggering drug resistance. Developing dual-target tyrosine kinase inhibitors for VEGFR and PDGFR can greatly improve the anti-angiogenesis and antitumor activities. Cediranib (AZD2171, **1o**) is one of the most potent multi-target anti-angiogenesis drugs with the inhibitory activity of 5 nM for both VEGFR-2 and PDGFR-β [26, 27]. Compound **1p** is a phenylurea derivative of 4-substituted quinazoline with inhibitory activities of 2.2 nM and 3.6 nM for VEGFR-2 and PDGFR, respectively [28].

An arylbenzothiazole derivative **1q** demonstrates high inhibitory activities with the respective IC_{50} values of 60 nM, 170 nM and 540 nM for VEGFR2, PDGFR-β and TIE2 *in vitro* [29]. The pyrazole derivative **1r** has a potent

and balanced profile against PDGFR and VEGFR-2 with the respective IC_{50} values of 4 nM and 8 nM. It has the potential to become an anti-angiogenic drug in the clinic [30]. Urea derivatives, synthesized by Raveza and co-workers [31], allowed a significant increase in the inhibitory effects on the growth of three cancer cell lines PC3, HT29 and MCF7. Such compounds are highly potent inhibitors of VEGFR (1, 2 and 3), PDGFR-β and c-KIT with the IC_{50} values in the nanomolar range. Among them, the potent multi-kinase inhibitor **1s** inhibits angiogenesis by preventing tube formation and inhibiting endothelial cell invasion.

Synthesis of quinazolinones and 4-anilino(or phenoxy)quinazolines

Methods based on intermediary of 4(3*H*)-quinazolinones for synthesis of 4-anilino(or phenoxy)quinazolines

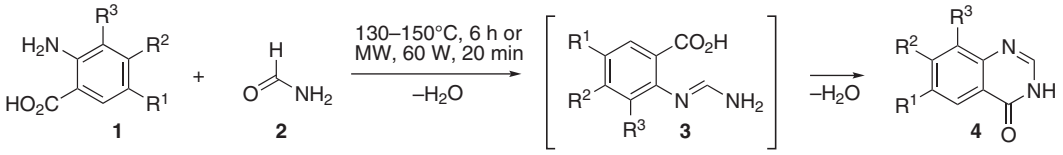
4-Anilino(or phenoxy)quinazoline compounds demonstrate various useful biological and medicinal activities. The most common synthetic approach to these compounds involves the preparation of the intermediate 4-chloroquinazolines from 4(3*H*)-quinazolinones followed by treatment with anilines or phenols. Many synthetic methods for 4(3*H*)-quinazolinones have been reported [32]. The most common method for preparation of 4(3*H*)-quinazolinones **4** is based on the Niementowski reaction (Scheme 1). This reaction involves the fusion of anthranilic acid derivatives **1** with formamide **2** which generates an *o*-amidine intermediate **3**. The procedure usually requires high temperatures and a tedious workup. To address these problems, Besson and co-workers [33] used microwave irradiation which improved the yield and decreased the reaction time.

Compound **5** (Scheme 2) was prepared by Shao and co-workers [34] under microwave irradiation from *m*-trifluoromethylaniline (**8**) and 6,7-dimethoxy-4-chloroquinazoline (**6**). Compound **6** was obtained by treatment of 6-aminoveratric acid (**7**) with formamide in the presence of phosphorus oxychloride. This reaction apparently involves generation of a 4(3*H*)-quinazolinone as a transient intermediate product.

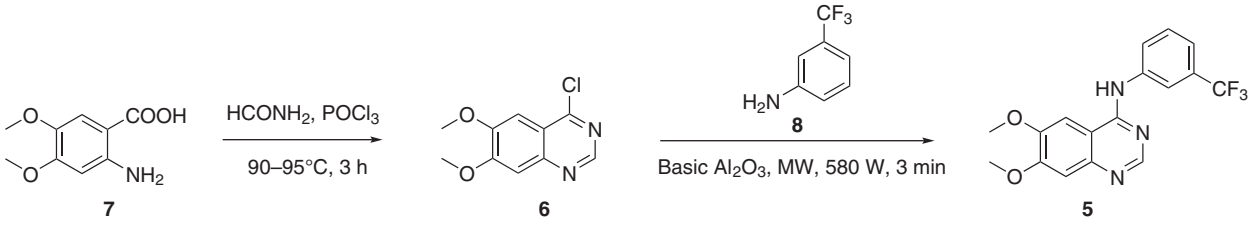
4(3*H*)-quinazolinones **9** were obtained by the reaction of substituted aromatic *o*-aminonitriles **10** with aldehydes in the presence of a base [35]. This transformation involves consecutive addition, intramolecular Pinner reaction, Dimroth rearrangement and oxidative dehydrogenation reactions. This synthesis has the advantages of readily available starting materials, mild reaction conditions and high yields of products (Scheme 3).

A microwave-assisted synthesis in an aqueous medium of quinazoline derivatives was developed [36]. Treatment of 2-aminobenzamide (**11**) with an excess of chloroacetyl chloride (**12**) under microwave irradiation furnished the intermediate 2-chloroacetamide **13**. The crude product was isolated and directly cyclized in the presence of K_2CO_3 in water, under microwave irradiation, leading to the expected product **14** (Scheme 4).

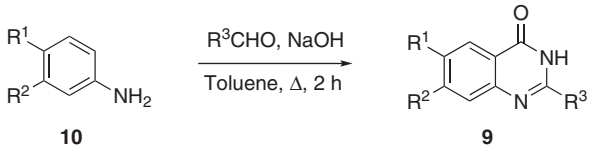
4-Anilino-7-nitroquinazoline (**18**) was synthesized [37] under microwave irradiation from aniline (**17**) and 7-nitro-4-chloroquinazoline (**16**). Using 4-nitroanthranilic acid (**15**) as the starting material, compound **16** was smoothly obtained through the Niementowski reaction followed by chlorination (Scheme 5).



Scheme 1



Scheme 2



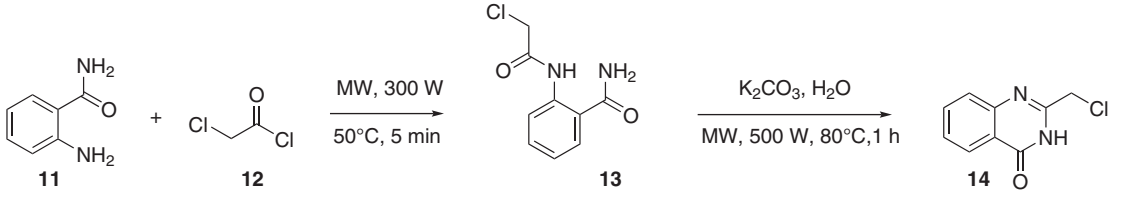
Scheme 3

4-Chloroquinazoline (**21**) was prepared from 2-aminobenzonitrile (**19**). Compound **19** was first converted to quinazolin-4(3*H*)-one (**20**) by acid-catalyzed cyclization with formic acid under microwave irradiation. Treatment of **20** under microwave irradiation with an excess amount of $POCl_3$ in *N*,*N*-diethylamine yielded the product **21** [38] (Scheme 6).

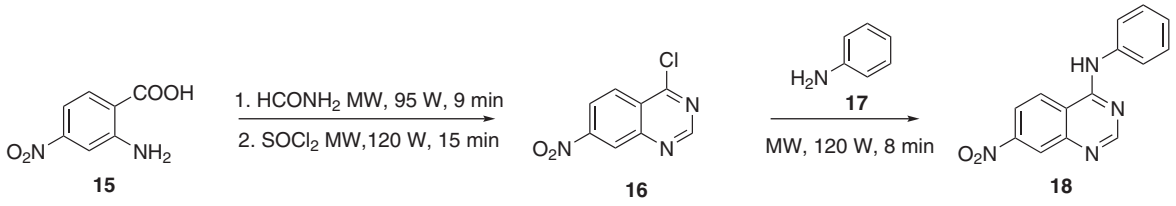
Ighilahriz and co-workers [39] developed a heteropolyacid-catalyzed method for the synthesis of 4(3*H*)-quinazolinones **24** by cyclocondensation of anthranilic acid (**8**), ortho ester **23** and substituted anilines **22**. This is a microwave-assisted, solvent-free, rapid and high yield reaction. The Keggin-type heteropolyacids are effective catalysts for this acid-catalyzed reaction (Scheme 7).

A zinc-catalyzed oxidation of 2-aminobenzamide (**25**) with a benzyl alcohol **26** was developed by Sharif et al. [40]. Various quinazolinones **27** were obtained in moderate to good yields. Treatment of aromatic aldehydes **28** with 2-aminobenzamide **25** under catalyst-free conditions afford the same products **27**. Surprisingly, water is also a good medium for this reaction (Scheme 8).

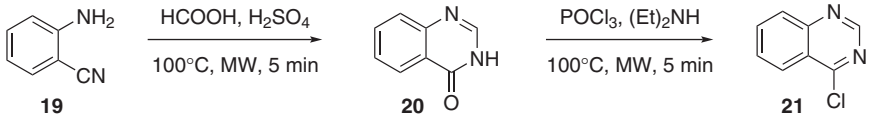
Metal-catalyzed Ullmann *N*-arylation can be used to construct *N*-heterocycles. Liu and co-workers [41] reported a simple, practical and efficient procedure for the preparation of quinazolinone derivatives under mild copper-catalyzed conditions. The target products **31** were obtained from 2-halobenzoic acids **29** and acetamidine hydrochlorides **30**. Subsequently, they developed an



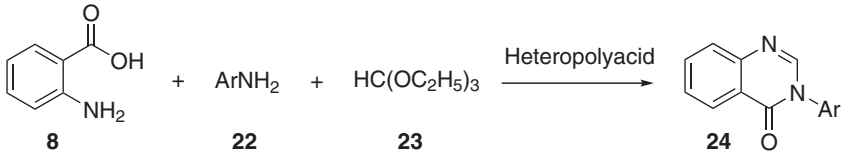
Scheme 4



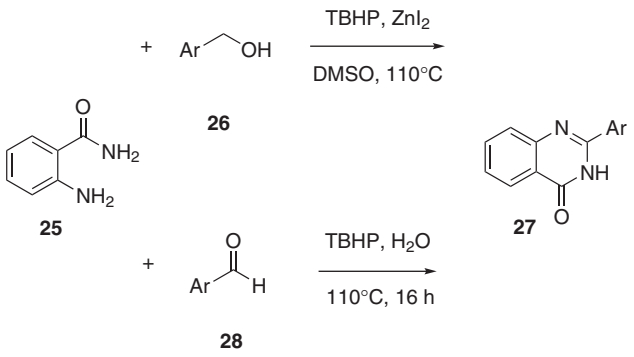
Scheme 5



Scheme 6



Scheme 7



Scheme 8

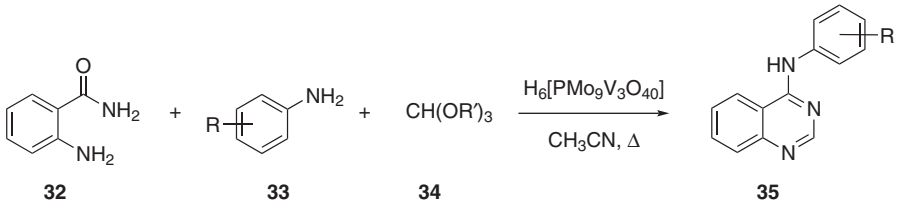
iron-catalyzed method for the reaction. This reaction provides a new method for the construction of diverse and practical molecules of potential biological and medicinal activities (Scheme 9).

Other synthetic methods

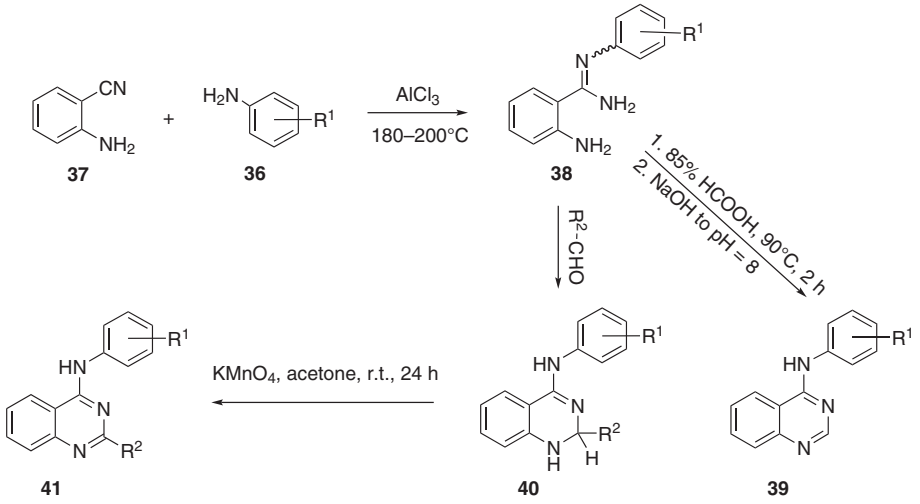
Heravi and co-workers [42] reported a one-pot method for the synthesis of 4-arylaminoquinazolines **35** by the reaction of anthranilamide (**32**), substituted aromatic amines **33** and ortho esters **34** catalyzed by heteropoly-acid. The yield of the product **35** ranges from 80% to 95%. This method uses a simple workup and the catalyst is recyclable (Scheme 10).

Szczepankiewicz and co-workers [43] described the synthesis of a series of 2-substituted **41** and 2-unsubstituted 4-arylaminoquinazolines **39** (Scheme 11). Thus, the treatment of 2-anthranilonitrile (**37**) with substituted anilines **36** in the presence of aluminum chloride gave the corresponding 2-amino-*N*-arylbenzamidines **38**. Products **39** were obtained directly by heating compounds **38** in formic acid. The treatment of amidines **38** with aldehydes

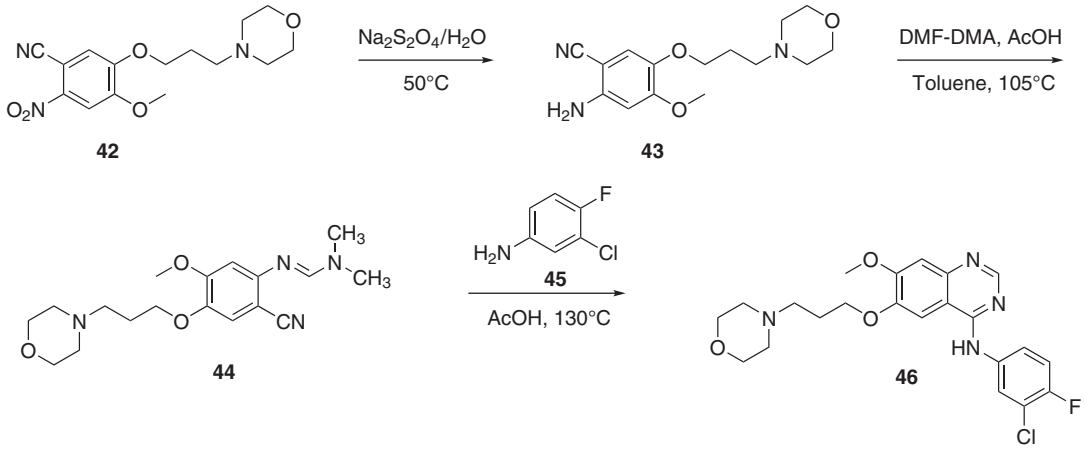
Scheme 9



Scheme 10



Scheme 11



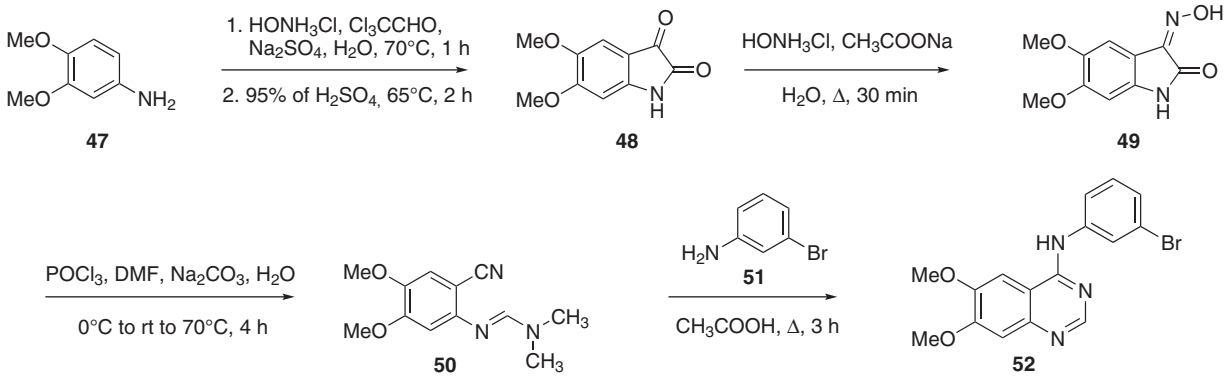
Scheme 12

afforded substituted 1*H*-2,3-dihydroquinazolines **40** readily oxidizable by treatment with potassium permanganate to quinazolines **41.**

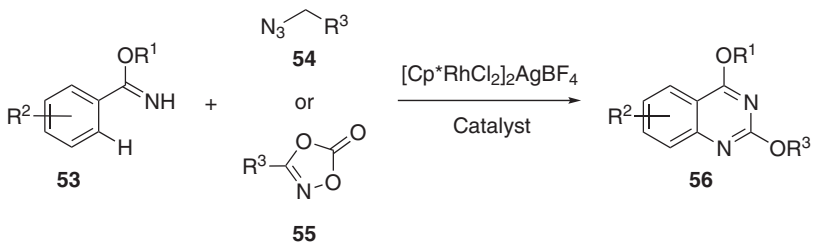
Chandregowda and co-workers [44] reported an approach for the construction of a quinazoline starting from reduction of *o*-nitrobenzonitrile **42** to anthranilonitrile **43.** Compound **43** was treated with a mixture of dimethylformamide (DMF) and dimethylacetamide (DMA) in toluene to give *N*,*N*-dimethylformamidine derivative **44.** The tyrosine kinase inhibitor gefitinib (**46**) was prepared by treatment of **44** with aniline **45** (Scheme 12).

Wang and co-workers [45] used 3,4-dimethoxyaniline (**47**) as the starting material for the synthesis of PD153035 (**52**) in a total yield of 50%. The intermediates **48–50** were synthesized as shown in Scheme 13. The final intermediate product **50** was treated with aniline **51** to produce the target compound **52.**

An annulation of benzimidates **53** with alkyl azides **54** or dioxazolones **55** for the preparation of quinazolines **56** was developed by Wang and co-workers [46, 47]. The operational simplicity, high atom efficiency and wide range of substrate scope make this method useful for the



Scheme 13



Scheme 14

practical preparation of phenoxy-substituted quinazoline derivatives (Scheme 14).

Conclusions

In this paper, quinazoline inhibitors of tyrosine kinases including their synthesis are summarized. Modifications in the structure of quinazoline class of antitumor agents are mainly focused on introducing the side chains at the 6- and 7-positions of 4-anilino(or phenoxy)quinazoline. The use of bioisosterism, reactive splicing methods and computer-aided drug design are also important directions for optimizing the structure of the compounds.

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