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Novel EGFR inhibitors prepared by combination of dithiocarbamic acid esters and 4-anilinoquinazolines

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ABSTRACT

On the basis of combination strategy, a novel series of EGFR inhibitors were designed and synthesized by combination of dithiocarbamic acid esters and 4-anilinoquinazolines. The effect of the synthesized compounds on cell proliferation was evaluated by MTT assay in three human cancer cell lines: MDA-MB-468, SK-BR-3 and HCT-116. Two compounds (**11d** and **11f**) were found more potent against all three cell lines and five compounds (**11a**, **11d–11g**) were found more potent against both MDA-MB-468 and SK-BR-3 than Lapatinib. SAR studies revealed that the substituents on C6 and C7 positions of quinazoline, the amine component of dithiocarbamate moiety and the linker greatly affected the activity. This work provides a promising new strategy for the preparation of potent tyrosine kinase inhibitors.

The epidermal growth factor receptors (EGFR) are a member of the ErbB receptor family of tyrosine kinases (TK) that are overexpressed in several human solid tumors. They are often associated with more aggressive disease and poorer clinical outcome.[1,2] Therefore, EGFR as a target of anticancer drugs has received much attention in the past decade. A series of EGFR inhibitors with different molecular scaffolds have been discovered. Among them, 4-anilinoquinazolines plays a key role and have been extensively studied.[3] As shown in Figure 1, Gefitinib (**1**) and Erlotinib (**2**) have been approved for the treatment of non-small-cell lung cancer (NSCLC).[4–11] Lapatinib (**3**), a potent dual inhibitor of ErbB-1 and ErbB-2, was approved in 2007 for treating breast cancer.[12] Many other 4-anilinoquinazoline derivatives are still under evaluation in clinical trials for the treatment of cancer (**4–6**).[13] Nevertheless, it is still necessary to develop novel EGFR targeting therapeutic agents with enhanced potency that can overcome drug resistance.

During the past decade, the study on the SAR of quinazoline EGFR inhibitors mainly focused on the modification of the C4 arylamino group. In recent years, the substituents at C6 position of quinazoline have received increasing attention in the development of more potent dual or multi-target inhibitors. The representative substituents at C6 position of quinazoline are listed in Figure 2. Almost all substituents were designed to bind with the –SH of Cys773 in EGFR through hydrogen bonding (Fig. 2, **I**)[14–16] or covalent bonding (Fig. 2, **II**).[17–19]

Recently, dithiocarbamic acid esters, a common class of organic molecules, have also attracted great attention due to their cancer chemopreventive and anticancer action.[20,21] It was reported that when a suitable molecular scaffold was incorporated into dithiocarbamic acid esters as a key pharmacophore, the molecule showed significant anticancer activity, such as thalidomide dithiocarbamates,[22] chromones dithiocarbamates,[23] and quinazolinone dithiocarbamates (Fig. 3 and entries **7–9**).[24] In our effort to seek for new kinds of anticancer drugs, we have identified a novel dithiocarbamate compound **10** (990207) with potent anticancer activity (Fig. 3 and entry 10).[25]

Considering the SAR of quinazoline EGFR inhibitors and the research progress on dithiocarbamic acid esters, we designed and synthesized a new kind of EGFR inhibitors **11** by combining different dithiocarbamic acid esters and selected quinazoline scaffolds with two kinds of linkers (Fig. 4).

The synthesis of compounds **11a–11c** is shown in Scheme 1. The quinazoline-4,6-diol **13** was prepared via Neimentowaki synthesis by heating **12** in formamide at 150 °C. Acetyl protection of the phenolic hydroxyl group of **13** with acetic anhydride gave **14**. Chlorination of **14** using thionyl chloride afforded the intermediate **15**. Coupling **15** with appropriate anilines yielded compounds **16a–16c**. Subsequent hydrolysis of the acetyl group using aqueous ammonia in methanol gave the corresponding C6-OH quinazolines **17a–17c**. Alkylation of the C6-OH of **17a–17c** with 1-bromo-3-chloropropane gave the corresponding ethers **18a–18c**. Finally, the target compounds **11a–11c** were prepared according to our established method by the reaction of compounds **18a–18c** with carbon disulfide and 1-methylpiperazine in the presence of anhydrous potassium phosphate.[25]

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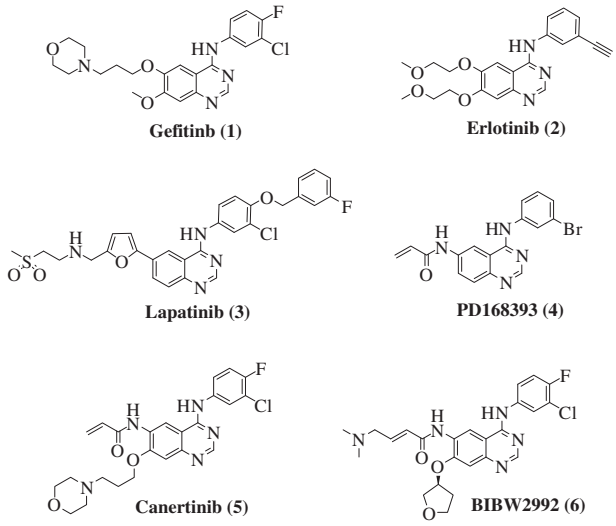


Figure 1. Representative inhibitors of EGFR tyrosine kinase.

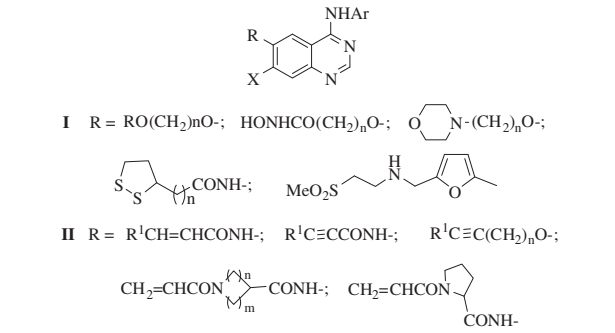


Figure 2. Representative substituents at C6 position of quinazoline EGFR inhibitors.

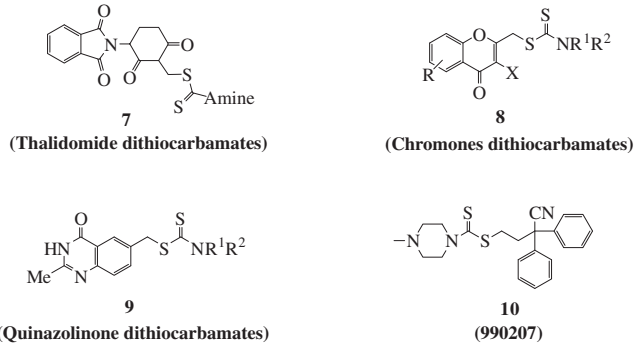


Figure 3. Structures of some dithiocarbamates with anticancer activities.

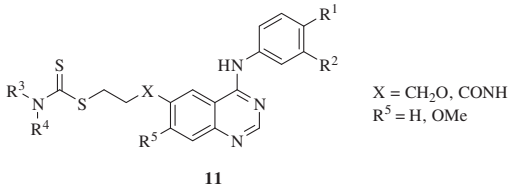
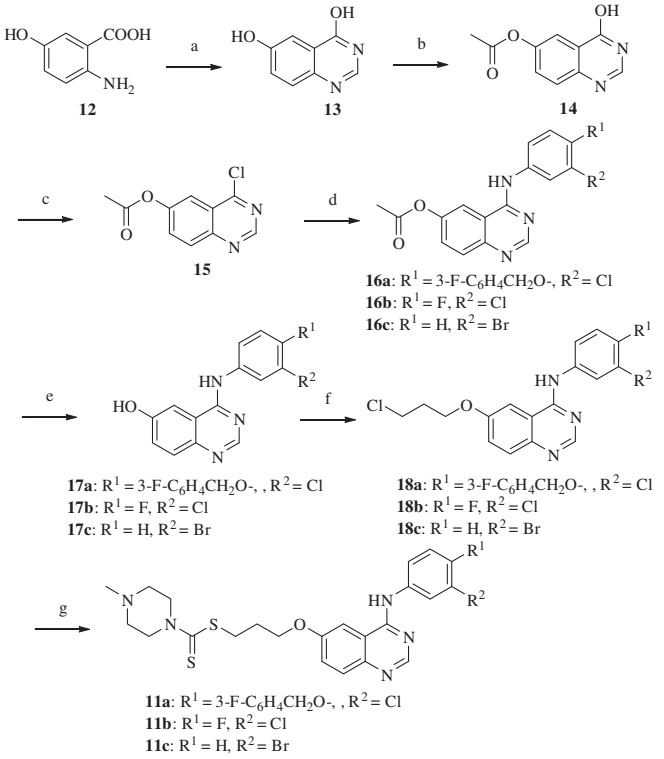
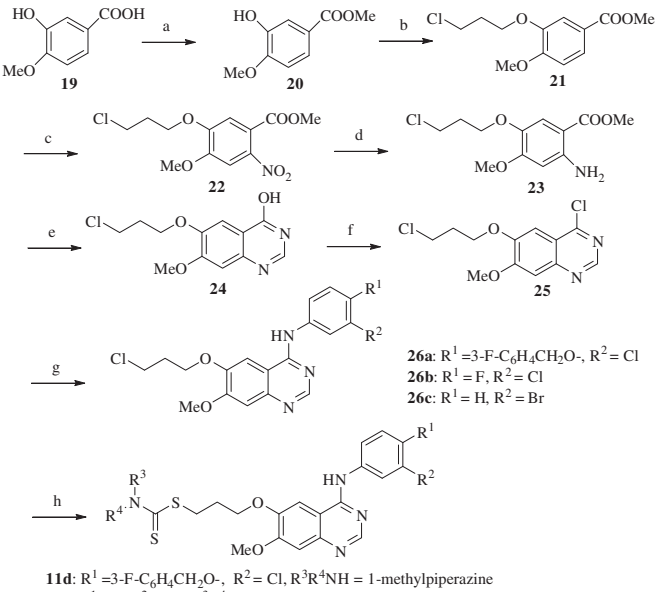


Figure 4. The structure of compounds **11**.



Scheme 1. Synthesis of compounds **11a–11c**. Reagents and conditions: (a) H_2NCHO, 150 °C; (b) Ac_2O, pyridine; (c) $SOCl_2$, DMF, reflux; (d) *i*-PrOH, aniline, Et_3N; (e) ammonia, MeOH; (f) $ClCH_2CH_2CH_2Br$, K_2CO_3, TBAB, CH_3CN, reflux; (g) CS_2, 1-methylpiperazine, K_3PO_4, DMF.



Scheme 2. Synthesis of compounds **11d–11j**. Reagents and conditions: (a) MeOH, $SOCl_2$; (b) $ClCH_2CH_2CH_2Br$, K_2CO_3, TBAB, CH_3CN, reflux; (c) HNO_3, H_2SO_4, $CHCl_3$; (d) Fe, NH_4Cl, MeOH/H_2O, reflux; (e) H_2NCHO, $POCl_3$, 90 °C; (f) $SOCl_2$, DMF, reflux; (g) *i*-PrOH, aniline, Et_3N; (h) CS_2, R^3R^4NH, K_3PO_4, DMF.

The target compounds **11d–11j** were prepared as shown in Scheme 2. Esterification of the starting material 3-hydroxy-4-methoxybenzoic acid **19** in the presence of thionyl chloride and methanol at ambient temperature gave **20**. Compound **20** was