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Design, synthesis and pharmacological evaluation of 6,7-disubstituted-4-phenoxyquinoline derivatives as potential antitumor agents

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ABSTRACT

Two series of 6,7-disubstituted-4-phenoxyquinoline derivatives bearing 2,4-imidazolinedione/pyrazolone scaffold were designed, synthesized and evaluated for their c-Met kinase inhibition and cytotoxicity against HT-29, H460, A549, MKN-45, and U87MG cancer cell lines *in vitro*. The pharmacological data indicated that most of the tested compounds showed moderate to significant cytotoxicity and high selectivity against HT-29, H460 and A549 cancer cell lines as compared with foretinib. The SAR analyses indicated that compounds with halogen groups, especially trifluoromethyl groups at 2-position on the phenyl ring (moiety B) were more effective. In this study, a promising compound **17** (c-Met IC_{50} = 2.20 nM, a multi-target tyrosine kinase inhibitor) showed the most potent antitumor activities with IC_{50} values of 0.14 μM, 0.18 μM, 0.09 μM, 0.03 μM, and 1.06 μM against HT-29, H460, A549, MKN-45, and U87MG cell lines, respectively.

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1. Introduction

c-Met kinase inhibitors have recently become an attractive therapeutic target for cancer therapy and it normally activated by binding its natural ligand hepatocyte growth factor (HGF), also known as scatter factor (SF). The binding of HGF to c-Met induces several complex signaling pathways and results in cell proliferation, motility, migration, and survival [1–3]. Moreover, c-Met has been found to be overexpressed or mutated in human cancers, especially correlated with advanced disease stage and poor prognosis. As a result, c-Met has attracted considerable attention as a potential target for cancer treatment [4–6].

Recently, a number of new 6,7-disubstituted-4-phenoxyquinoline derivatives with excellent antitumor activity have been reported. Many of these derivatives are being marketed or under clinical/preclinical studies, such as cabozantinib (**1**), Foretinib (**2**) and AM 7 (**3**) (Fig. 1) [7,8]. Cabozantinib (**XL-184, 1**), a typical multikinase inhibitor (c-Met included) bearing quinoline pharmacophore, was approved by U.S. FDA in November 2012 for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC) [9]. Foretinib (**XL880, 2**), which is currently undergoing phase III studies for different cancer types, is a novel oral multikinase inhibitor targeting c-Met, VEGFR, RON, KDR and Flt-1. As shown in **Figure 1**, the main modification of these quinoline derivatives was focused on the 5-atom linker containing hydrogen-bond donors or acceptors between moiety A and B, which is known as **"5 atoms regulation"** in our previous study [10]. In addition, the modifications of the A moiety usually occurred at 7-position of quinoline, while the methoxy group was replaced by a water-soluble fragment, such as 3-morpholinopropoxy group. These structural features indicated that exploring a satisfactory linker was a practicable way of designing new quinoline derivatives. In our previous study, we had introduced 1,4-dihydroquinoline, *N*-arylidene semicarbazide and quinoline scaffolds as part of the 5-atom linkers, and the resulting derivatives (**4**–**6,** Fig. 1) showed excellent antitumor activity [11–13].

Compounds containing *N*-Aryl-pyrazolone-4-imino and 2,4-imidazolinedione framework displayed a multitude of biological activities, including antitumor, antibacterial, antihypertensive, antiplatelet and anti-inflammatory activities [14–17]. Remarkably, this framework was widely used as a building block in the design of anticancer agents because of its ability to form hydrogen-bonding interactions with drug targets. For example, compound **7** and **8** (Fig. 2), as a potent catalytic inhibitor of human telomerase, was reported as large ribonucleoprotein complex of reverse transcriptase enzyme [18,19]. It was interested that the *N*-Aryl-pyrazolone-4-imino and 2,4-imidazolinedione framework conformed to the rule of **"5 atoms regulation"** and contained both hydrogen-bond donor and acceptor, which indicated that it was a satisfactory linker.

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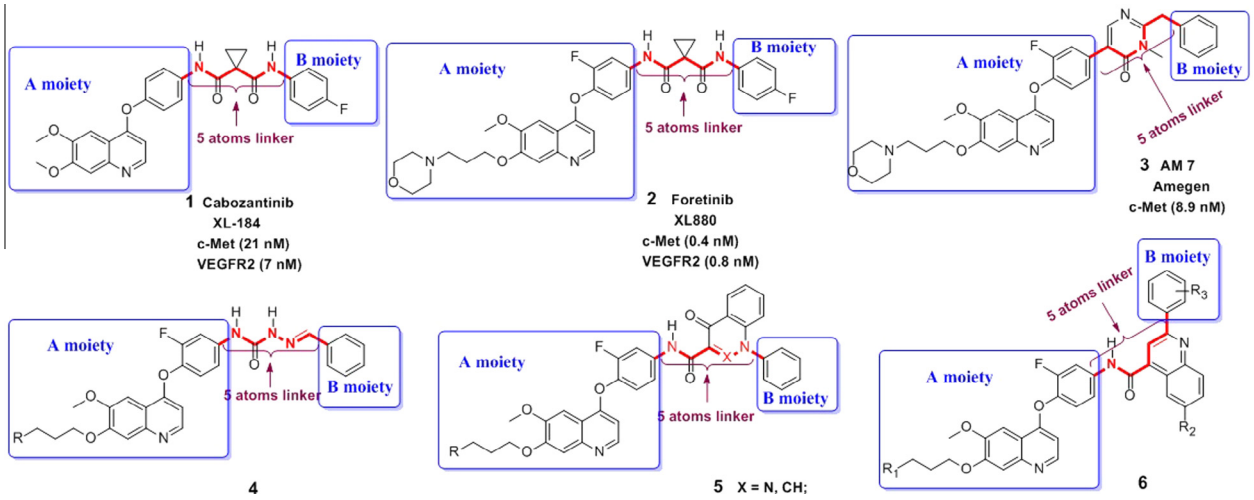

Fig. 1. Structures of small-molecule c-Met inhibitors based on the 6,7-disubstituted-4-phenoxyquinoline scaffold.

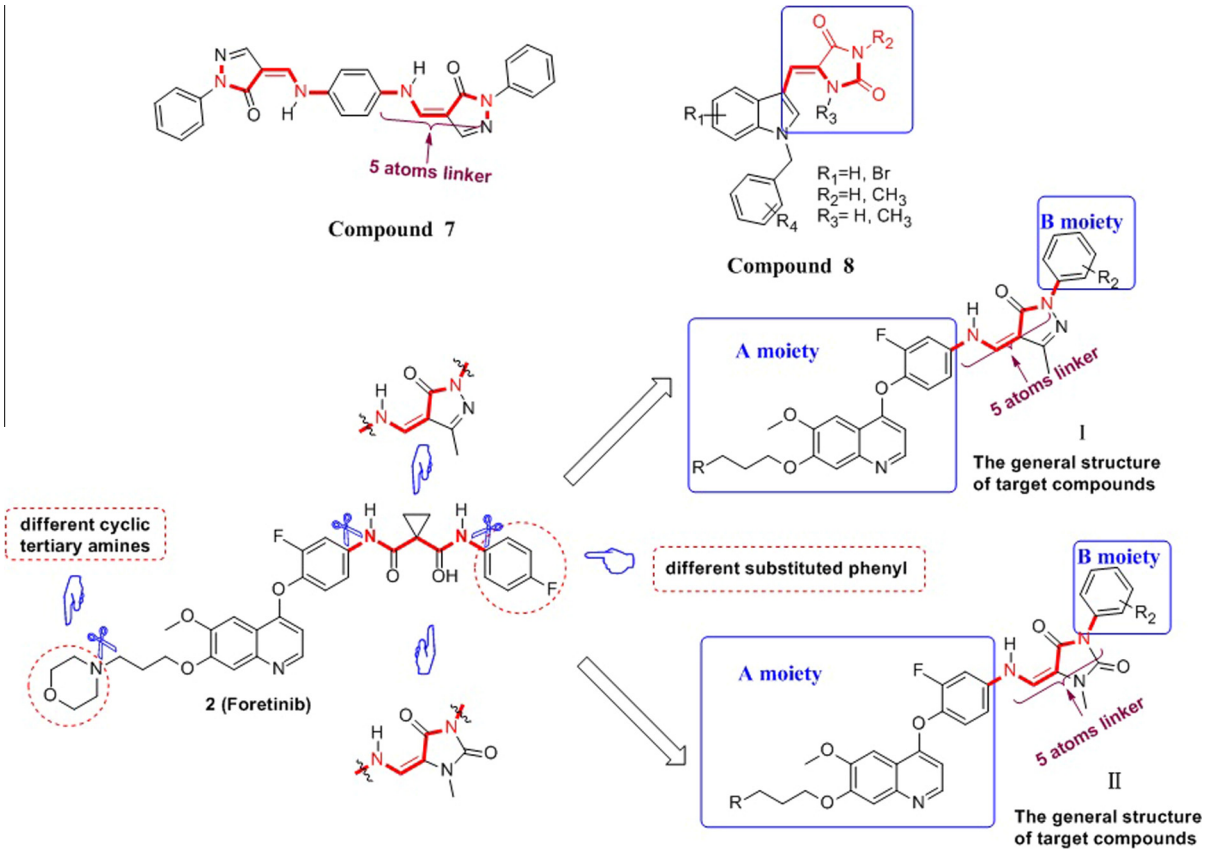

Fig. 2. The structure of compound **7**, **8** and the target compounds.

Therefore, we selected *N*-Aryl-pyrazolone-4-imino and 2,4-imidazolinedione framework as the 5-atom linker to obtains two series of novel 6,7-disubstituted-4-phenoxyquinoline derivatives (**I, II** Fig. 2). Meanwhile, at the 7-position of quinolines, a three-carbon tether which contained different cyclic tertiary amines were introduced, such as 4-methyl piperidinyl, piperidinyl, 4-methyl piperazinyl and pyrrolidinyl group. Additionally, various substituents (R_2) were introduced into the phenyl ring (B moiety) to investigate their effect on activity. In this paper, the synthesis of these quinoline derivatives was reported and their *in vitro* anticancer activities against five human cancer cell lines included the A549 (human lung adenocarcinoma), H460 (human lung cancer), HT-29 (human colon cancer), MKN-45 (human gastric cancer) and U87MG (human glioblastoma), and c-Met kinase were evaluated, respectively.

2. Chemistry

2.1. Synthesis of 6,7-disubstituted-4-phenoxyquinolines

The key intermediates 6,7-disubstituted-4-phenoxyquinolines **8a–e** were synthesized using a convenient eight-step procedure

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