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Research paper

Design, synthesis and structure-activity relationships of novel 4-phenoxyquinoline derivatives containing 1,2,4-triazolone moiety as c-Met kinase inhibitors

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ABSTRACT

A series of novel 4-phenoxyquinoline derivatives containing 1,2,4-triazolone moiety were synthesized and evaluated for their *in vitro* cytotoxic activity against four cancer cell lines (HT-29, H460, A549 and MKN-45). Most of the compounds exhibited moderate-to-significant cytotoxicity. Compounds **33**, **37**, **39**, **44**, **46**, **47**, **53**, **55**, **61**, **64** and **66** were further examined for their inhibitory activity against c-Met kinase. The most promising compound **47** (with c-Met IC_{50} value of 1.57 nM) showed remarkable cytotoxicity against HT-29, H460, A549 and MKN-45 cell lines with IC_{50} values of 0.08 μM, 0.14 μM, 0.11 μM and 0.031 μM, respectively, and thus it was 1.1- to 2.3- fold more potent than foretinib. Their preliminary structure-activity relationships (SARs) studies indicate that electron-withdrawing groups on the terminal phenyl rings are beneficial for improving the antitumor activity.

1. Introduction

The understanding of molecular mechanism for cancer has been dramatically progressed over the last decade. Since it is known that cancer is mainly caused by abnormal increased expression or activation of oncogenes and the corresponding proteins, it is rational to target a protein that is a key component of the oncogenic pathway as protein-targeted cancer therapies. c-Met tyrosine kinase is encoded by proto-oncogene Met and is the only known high-affinity receptor for hepatocyte growth factor (HGF), also known as scatter factor [1–4]. The HGF/c-Met kinase pathway regulates cell growth, differentiation and proliferation [5,6], and overexpression or mutation of protein members of this pathway is a driving factor for numerous cancers [7–9]. To date, targeting the HGF/c-Met signaling pathway as a means of cancer therapy has become increasingly popular with a number of different therapeutic approaches undergoing clinical trials [10–12], among which small molecule c-Met inhibitors constitute the largest effort within the pharmaceutical industry.

Recently, a series of c-Met inhibitors with different molecular scaffolds have been discovered. Among them, 6,7-disubstituted-4-phenoxyquinolines play a key role and have been extensively studied. Many of these derivatives are already being marketed or are under clinical/preclinical studies, such as foretinib, cabozantinib, MG10, AM7 and Amgen (**1**-**6**, Fig. 1). These compounds are multikinase inhibitors, which belong to class II Met inhibitors [13–18]. A good example of these class II inhibitors is foretinib, which inhibits the kinase activity of c-Met (IC_{50} = 0.40 nM), as well as that of VEGFR-2 (IC_{50} = 0.86 nM), Ron (IC_{50} = 3.0 nM), FLT-3 (IC_{50} = 3.6 nM), c-Kit (IC_{50} = 6.7 nM), and PDGFRα/β (IC_{50} = 3.6/9.6 nM) [19]. Although these agents have been generally well characterized, clinical use has shown that these agents elicit unexpected and serious toxic effects in various organs [20]. Moreover, the more potent VEGFR activity in some class II Met inhibitors may lead to suboptimal dosing for Met inhibition in clinical applications because of VEGFR-related side effects [21]. Therefore, novel Met inhibitors with improved selectivity profiles, particularly to VEGFR-2, and minimal side effects should be developed.

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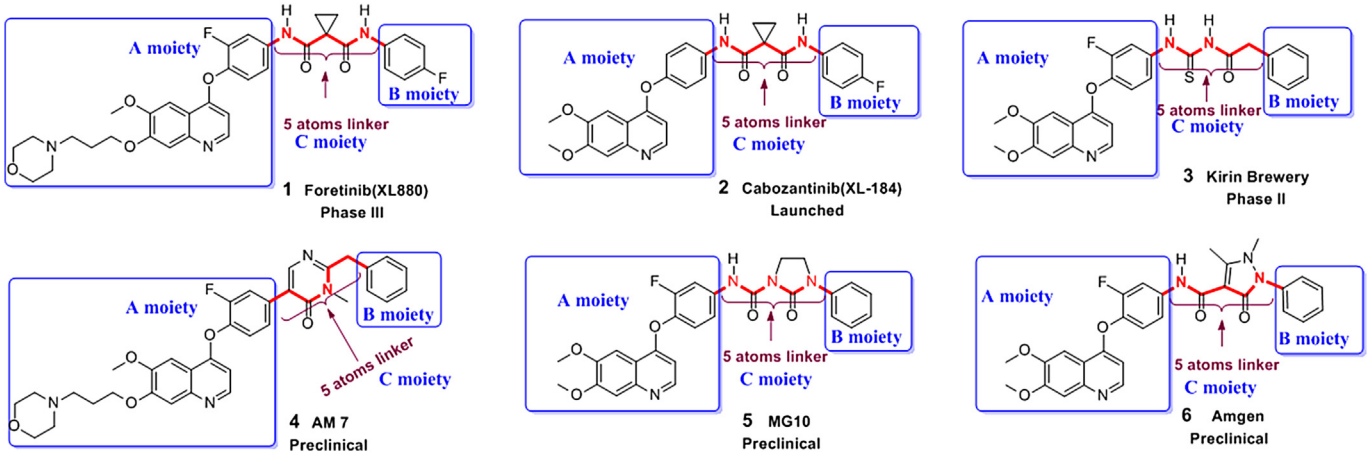

Fig. 1. Structures of small-molecule c-Met inhibitors.

As displayed in Fig. 1, most of the 6,7-disubstituted-4-phenoxyquinoline inhibitors may be disconnected into three units according to their structures and subunit functions. In previous researches, our group have designed and synthesized a series of 6,7-disubstituted-4-phenoxyquinoline derivatives **7**-**12** (Fig. 2), which showed excellent potencies [22–27]. The SAR studies about those compounds suggested that moiety A and moiety B (usually phenyl ring or substituted phenyl ring) appears to be critical for kinase activity. In contrast, the structure of moiety C is alterable, and various linear chains and heterocyclic rings can be introduced to the main chain of 5-atom linker (i.e., six chemical bonds distance between moiety A and B, as summarized recently by our team [27].), containing hydrogen-bond donors and acceptors. In the light of the results mentioned above, the 5-atom linker is the key structural motif which is considered to be the primary modification position. Moreover, derivatives **9** and **10** with a 5-membered heterocycle in the linker, exhibits modest selectivity (53 fold and 172 fold) to VEGFR-2. Therefore, we postulated that moiety C could be modified with 5-membered heterocycle and moiety A and B could be reserved. Such processes may be effective strategies that could be used to discover selective class II Met inhibitors. With the goal of finding more selective class II Met inhibitors, we introduced 1,2,4-triazolone framework, bearing one amide bond as a part of the 5-atom linker between moiety A and B via cyclization strategy (Fig. 3). The novel target scaffold was docked to the c-Met binding pocket (PDB: 3LQ8) and overlay results showed that the conformation of this novel scaffold is well consistent with foretinib's binding conformation, which suggested that a 5-oxo-4,5-dihydro-1*H*-1,2,4-triazole- 3-carboxamide moiety could serve as a scaffold from which to build a novel series of c-Met inhibitors (Fig. 4).

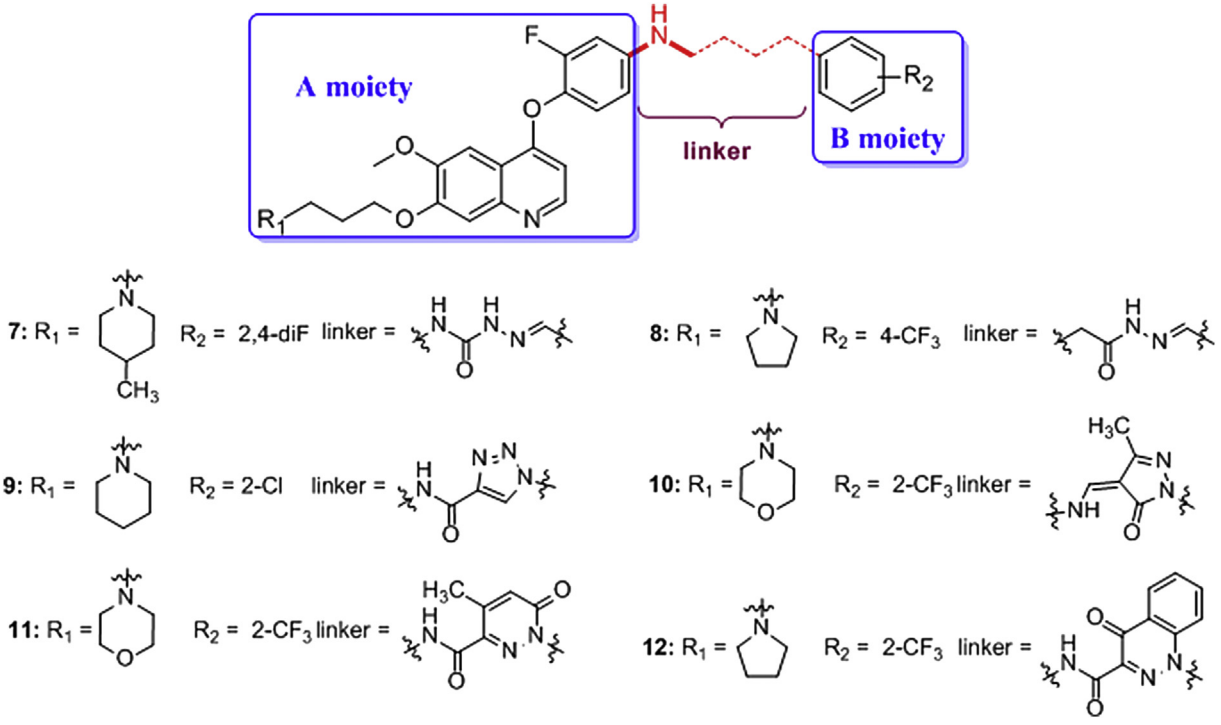

Fig. 2. Our previous work on small-molecule c-Met kinase inhibitors.