European Journal of Medicinal Chemistry 119 (2016) 96–108

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Discovery of a novel 6,7-disubstituted-4-(2-fluorophenoxy)quinolines bearing 1,2,3-triazole-4-carboxamide moiety as potent c-Met kinase inhibitors

Mingmei Liu, Yunlei Hou, Weile Yin, Shunguang Zhou, Ping Qian, Zhuang Guo, Liying Xu, Yangfang Zhao*

Key Laboratory of Structure-Based Drug Design and Discovery (Shenyang Pharmaceutical University), Ministry of Education, 103 Wenhua Road, Shenhe District, Shenyang 110016, PR China

ARTICLE INFO

Article history:
Received 17 July 2015
Received in revised form
12 February 2016
Accepted 12 April 2016
Available online 23 April 2016

Keywords:
c-Met
Synthesis
Antitumor activity
Quinoline derivatives

ABSTRACT

A series of 6,7-disubstituted-4-(2-fluorophenoxy)quinoline derivatives possessing 1,2,3-triazole-4-carboxamide moiety were designed, synthesized and evaluated for their *in vitro* cytotoxic activities against four typical cancer cell lines (A549, H460, HT-29, and MKN-45). Most compounds showed moderate-to-excellent antiproliferative activity. Compounds **32, 36, 37, 45, 51,** and **52** were further examined for their inhibitory activity against c-Met kinase. The promising compound **37**, with a c-Met IC_{50} value of 2.27 nM, was identified as a multitargeted receptor tyrosine kinase inhibitor. The analysis of their structure–activity relationships indicated that compounds with EWGs, especially chloro group, at 2-position on the phenyl ring (moiety B) have potent antitumor activity.

1. Introduction

Mesenchymal–epithelial transition factor (c-Met), a member of a structurally distinct family of receptor tyrosine kinases (RTK) [1,2], was discovered in 1984 as an oncogenic fusion protein TPR-MET [3]. In normal cells, the activation of c-Met occurs through the extracellular binding to its natural ligand, hepatocyte growth factor/scatter factor (HGF/SF). A variety of human cancers involve aberrant HGF/SF or c-Met expression or the activation of c-Met kinase mutations [4]. Consequently, inhibiting the activation of c-Met activity is a potentially impactful approach to the treatment of cancers caused by the activation of the c-Met [5].

There has been a significant interest in the development of small molecule c-Met inhibitors for the treatment of cancer [6]. Several quinoline derivatives have been reported recently as small-molecule c-Met inhibitors such as Foretinib (**1**), Cabozantinib (**2**) and AM 7 (**3**) (Fig. 1). These compounds are multikinase inhibitors, which usually exert strong inhibitory effect on VEGFR and other homological kinases as well [7–10]. From the structures, we can see that their main modification was focused on the 5-atom linker containing hydrogen-bond donors or acceptors between moiety A and B, which is known as "**5-atom regulation**". In the light of the results mentioned above, our research group has introduced different 5-atom linkers, such as 1, 4-dihydrocinnoline-3-carboxamide, pyridine/pyrimidine-based, *N*-acylhydrazine and pyrimidine-2, 4,6-trione and the resulting derivatives **7**–**10** (Fig. 2) showed excellent potency [11–14].

To our knowledge, compounds bearing 1,2,3-triazole-4-carboxamide fragment have been reported to exhibit a large field of biological activities, including antitumor, antibacterial, and anti-inflammatory activities, etc (**11**–**13,** Fig. 3) [15–20]. Therefore, we introduced 1,2,3-triazole-4-carboxamide fragment to the target quinoline derivatives as the 5-atom linker in an effort to provide more potent antitumor agents.

Taking Foretinib as the leading compound, we designed and synthesized a novel series of 6, 7-disubstituted-4-(2-fluorophenoxy) quinoline derivatives (Fig. 4), in which moiety A was preserved and the 1,2,3-triazole-4-carboxamide fragment was attached into the C-4′ position.

The target compounds synthesized were evaluated for their inhibitory activities against c-Met kinase and antiproliferative activities against 4 cancer cell lines including the HT-29 (human colon

* Corresponding author.
E-mail address: yanfangzhao@126.com (Y. Zhao).

http://dx.doi.org/10.1016/j.ejmech.2016.04.035
0223-5234/

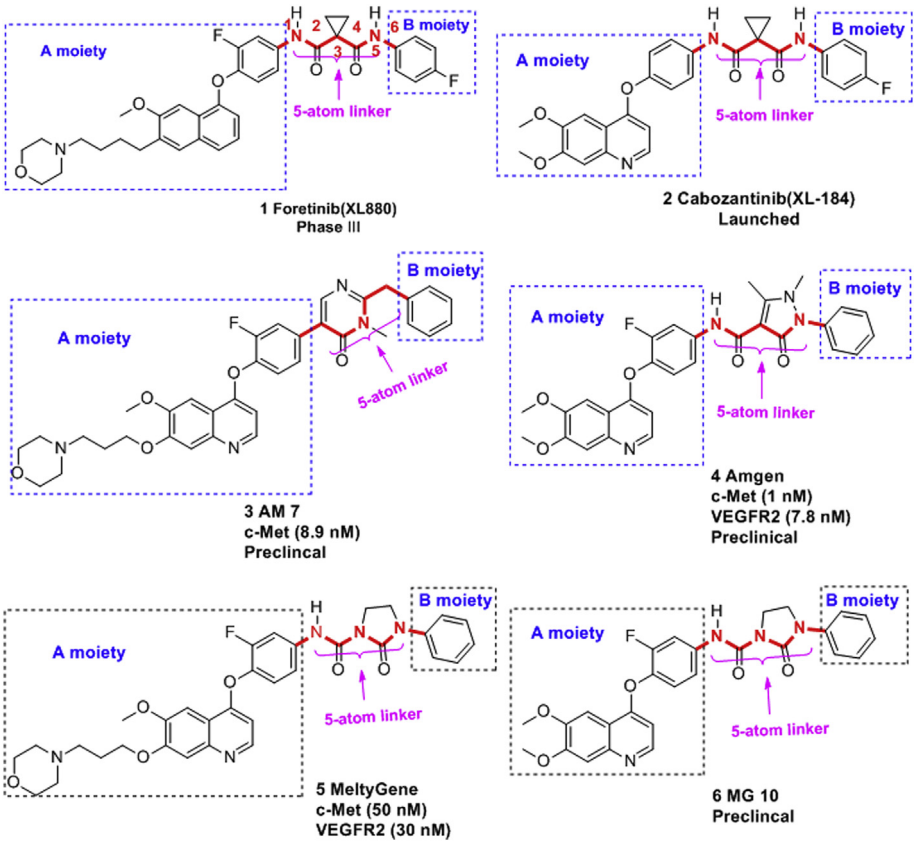

Fig. 1. The representative 4-phenoxyquinoline derivatives as small-molecule c-Met kinase inhibitors.

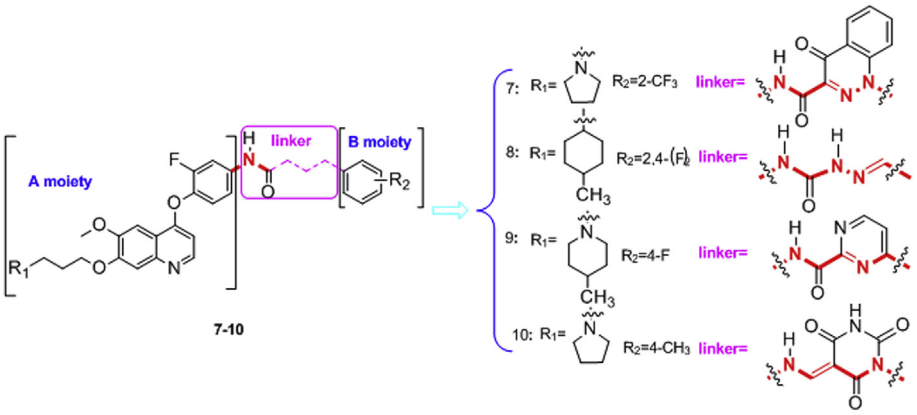

Fig. 2. Representative compounds in our previous work as small-molecule c-Met kinase inhibitors.

cancer), H460 (human lung cancer), A549 (human lung adenocarcinoma), MKN-45 (human gastric cancer).

2. Chemistry

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

The key intermediates 6,7-disubstituted-4-phenoxyquinolines **21a**–**e** were synthesized using a convenient eight-step procedure starting from 1-(4-hydroxy-3-methoxyphenyl)ethanone as shown in Scheme 1, which was illustrated in detail in our previous study [21,22].

2.2. Synthesis of the target compounds

The synthesis of target compounds **26**–**56** is summarized in Scheme 2. Condensation of commercially available substituted phenylamines with sodium nitrite ($NaNO_2$) and sodium azide (NaN_3) in H_2O/HCl at 0 °C resulted in high yield of intermediates **22a-h** as brown oil. Acylation of the aryl azides **22a-h** with 2-chloroacrylonitrile in water at 80 °C afforded intermediates **23a-h**, which were converted to acids **24a-h** using 10% sodium hydroxide solution at 80 °C for 4 h. Subsequently, intermediates **24a-h** were refluxed in toluene and $SOCl_2$ for 6 h to afford acyl chlorides **25a-h**, which were condensed with intermediates **21a-e** in the presence of sodium carbonate in dichloromethane at room