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Original article

Design and optimization of novel 4-(2-fluorophenoxy)quinoline derivatives bearing a hydrazone moiety as c-Met kinase inhibitors

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ABSTRACT

A series of 4-(2-fluorophenoxy)quinoline derivatives containing an acylhydrazone moiety were designed, synthesized and evaluated for their *in vitro* biological activities against c-Met kinase and five cancer cell lines (A549, H460, HT-29, MKN-45, and U87MG). Most compounds showed weak to excellent antiproliferative activity. The most promising analog, **40** (c-Met $IC_{50} = 1.86$ nM), displayed 1.3-, 6.8-, 1.5-, 3.5-fold increase against HT-29, H460, A549 and U87MG cell lines, respectively, compared with Foretinib. An analysis of structure-activity relationships revealed that an acylhydrazone scaffold with an unsubstituted sp^2 hybridized carbon adjacent to the 4-CF_3 phenyl ring is favorable for antitumor activity.

1. Introduction

Target-based therapies have significantly changed cancer treatment. Among the targets, the c-Met receptor tyrosine kinase and its natural ligand hepatocyte growth factor (HGF) have recently gained considerable attention [1]. The binding of HGF to c-Met induces several complex signaling pathways that promote cell proliferation, motility, migration, and survival [2–4]. These cellular activities are important during normal development and wound healing but can lead to cancer when the pathway is deregulated. For example, c-Met has been found to be overexpressed or mutated in human cancers, and in many instances, the overexpression of c-Met was demonstrated to correlate with advanced disease stage and poor prognosis [5–7]. Therefore, c-Met and its ligand HGF have become leading candidates for molecular targeted cancer therapies.

Several small-molecule c-Met inhibitors have recently been reported [8], including GSK's foretinib (**1**) [9], Kirin's acylthiourea (**2**) [10], and Exelixis's cabozantinib (**3**) (Fig. 1) [11]. Of these inhibitors, the modification usually occurs at the 7-position of quinoline and the "**5 atoms linker**" section. Using foretinib as a lead compound, we developed a series of 6,7-disubstituted-4-phenoxyquinoline-based c-Met inhibitors exemplified by compounds **4**–**6** (Fig. 1), which bear 2-arylquinoline-4-carboxamide, semicarbazones, and 4-arylpyridine-4-carboxamide fragments [12–14]. The antitumor activity of these compounds indicated that the different linkers of these quinoline derivatives are important for maintaining favorable enzyme activities and cellular potencies. In an ongoing effort to design novel c-Met inhibitors, a report from Sugen et al. [15], describing a series of indolinone hydrazides as potent c-Met inhibitors caught our attention. They reported that a representative compound, compound **7** (Fig. 2), was shown to inhibit c-Met activity with an IC_{50} of 54 nM. Furthermore, PAC-1 (**8**, Fig. 2), which contained an acylhydrazone moiety, was identified as the first procaspase activating compound that demonstrated promising anticancer properties both *in vitro* and in mouse xenograft models [16,17]. Consequently, we designed a series of novel c-Met inhibitors through the formation of a hybrid structure that contained the 6,7-disubstituted-4-phenoxyquinoline and an acylhydrazone moiety. In addition, different tertiary amines were introduced at the 7-position of quinolines as polar and water-solubilizing fragments. The outcome of this exercise was the formation of **I** (Fig. 3), which their structure-activity relationships (SARs) were further explored.

All compounds were evaluated for their antiproliferative activity *in vitro* against the following cell lines: HT-29 (human colon cancer), H460 (human lung cancer), A549 (human lung

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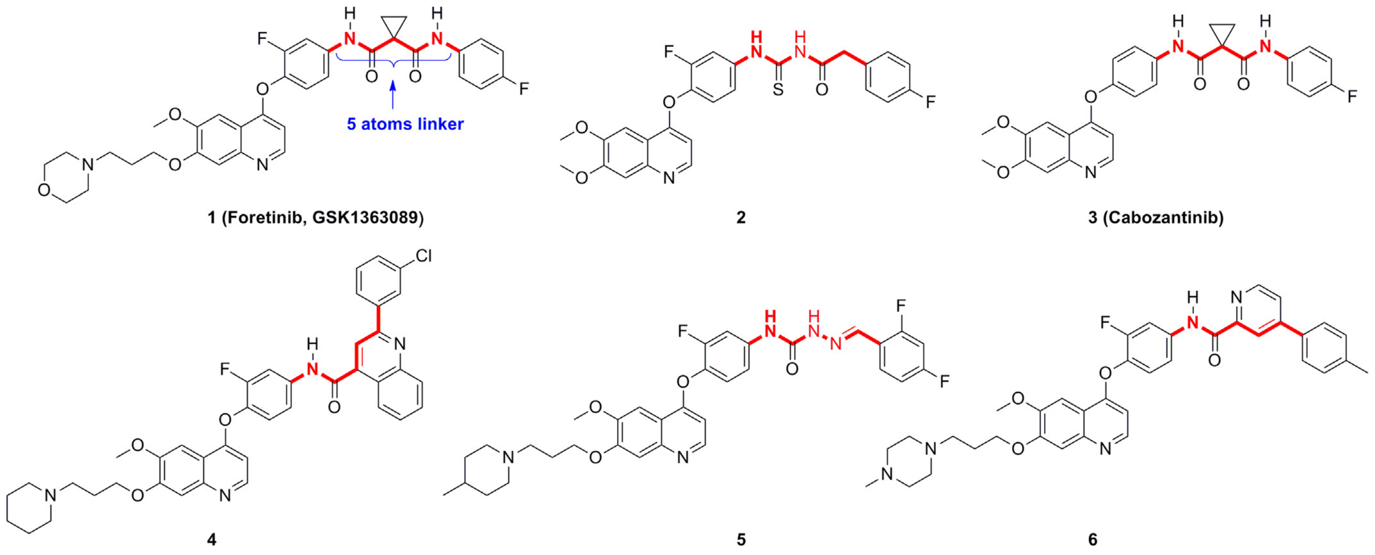

Fig. 1. Structures of small-molecule c-Met inhibitors.

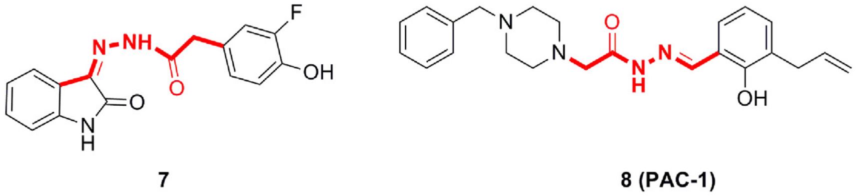

Fig. 2. Anticancer agents bearing hydrazone moiety.

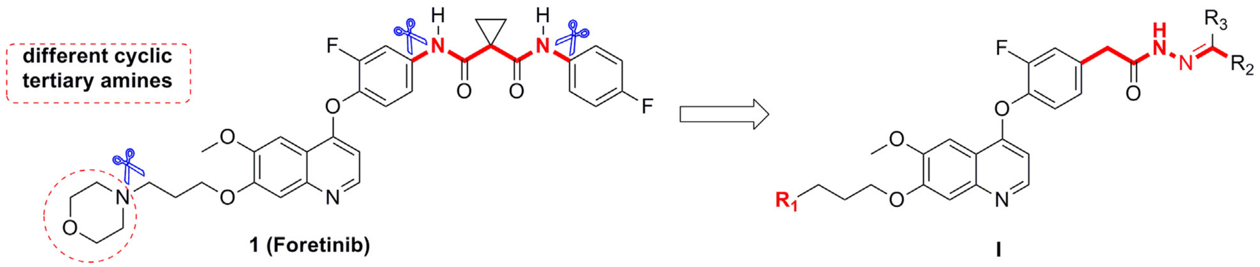

Fig. 3. General structure of the target compounds.

adenocarcinoma), MKN-45 (human gastric cancer), and U87MG (human glioblastoma). In addition, six potent compounds were evaluated for their inhibitory activity towards the c-Met enzyme. The results are illustrated in Tables 1 and 2.

2. Chemistry

On the basis of the above rationale, we necessitated a general method that allowed for the rapid preparation of target compounds (Scheme 1). The synthesis of intermediate **11** began with the hydrolysis of commercially available 3-fluoro-4-methoxyphenylacetonitrile by refluxing in EtOH/H_2O in the presence of KOH, subsequent O-demethylation by aluminum chloride in toluene followed by esterification with methanol [18]. As shown in Scheme 1, other key intermediates of 6,7-disubstituted-4-phenoxyquinolines, **17a**–**d**, were achieved in 6 steps from the commercially available 1-(4-hydroxy-3-methoxyphenyl)-ethanone, as illustrated in our previous study [12]. The obtained **17a**–**d** were etherified with **11** in chlorobenzene to provide purified compounds **18a**–**d**, which were subjected to hydrazinolysis with 80% hydrazine monohydrate in methanol at room temperature to yield **19a**–**d**. Finally, the target compounds were obtained via the condensation of **19a**–**d** with the appropriate aldehydes or ketones in ethanol at reflux with catalytic amounts of acetic acid.

The structures of the target compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and MS spectra. All target compounds might exist in the *E* or *Z* form due to the imino bond. Interestingly, the proton NMR spectrum revealed two sets of hydrogen resonance signals with a relative integral intensity ratio of approximately 2:3. For example, **40**, consisted of two CH=N*H* singlets, two C*H*=NH singlets, doubles of aromatic doublets, two C$\boldsymbol{H}_2$C=O singlets, and two OC$\boldsymbol{H}_3$ singlets (Fig. 4). The mixture of the two rotamers was obtained, and we were not able to separate them from the silica gel column chromatography.