Bioorganic & Medicinal Chemistry 21 (2013) 5246–5260

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Discovery and optimization of novel 4-phenoxy-6,7-disubstituted quinolines possessing semicarbazones as *c*-Met kinase inhibitors

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ARTICLE INFO

Article history:
Received 23 May 2013
Revised 10 June 2013
Accepted 11 June 2013
Available online 19 June 2013

Keywords:
c-Met
Kinase inhibitor
Anti-tumor
Quinoline
Semicarbazone

ABSTRACT

A novel series of N^1-(3-fluoro-4-(6,7-disubstituted-quinolin-4-yloxy)phenyl)-N^4-arylidenesemicarbazide derivatives were synthesized and evaluated for their *c*-Met kinase inhibition and cytotoxicity against A549, HT-29, MKN-45 and MDA-MB-231 cancer cell lines in vitro. Several potent compounds were further evaluated against three other cancer cell lines (U87MG, NCI-H460 and SMMC7721). Most of compounds tested exhibited moderate to excellent activity. The studies of SARs identified the most promising compound **28** (*c*-Met IC_{50} = 1.4 nM) as a *c*-Met kinase inhibitor. In this study, a promising compound **28** was identified, which displayed 2.1-, 3.3-, 48.4- and 3.6-fold increase against A549, HT-29, U87MG and NCI-H460 cell lines, respectively, compared with that of Foretinib.

1. Introduction

The *c*-mesenchymal-epithelia transition factor (*c*-Met) discovered in 1980s is a prototype member of the receptor tyrosine kinases (RTKs) subfamily.[1,2] Compared to normal *c*-Met/HGF signaling, aberrant *c*-Met kinase activity stimulates signaling pathways responsible for proliferation, invasion, migration, angiogenesis, survival, metastasis, and drug resistance.[3,4] Accordingly, deregulation of the *c*-Met/HGF signaling axis has been identified as a key contributing factor in a wide variety of human malignancies, including glioma, renal, lung, gastric, prostate and colorectal cancers.[5,6] Given the strong connection of abnormal *c*-Met/HGF signaling to human carcinomas, recently, developing its inhibitors have been actively pursued by researchers, especially small-molecule inhibitors targeting the catalytic domains of kinase.

Cabozantinib (Cometriq™, **1**), a quinoline-based multitargeted tyrosine kinase inhibitor,[7] was approved by U.S. FDA in November, 2012 for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC). In addition, a variety of small-molecule inhibitors have emerged in recent years, which included Kirin Brewery's acylthiourea (**2**), BMS-777607 (**3**), AM7 (**4**), Foretinib (GSK1363089, **5**) and Crizotinib (PF-02341066, **6**) (Fig. 1).[8–12]

Of the *c*-Met kinase inhibitors undergoing clinical trials or launched, compounds bearing quinoline pharmacophores exhibited excellent inhibitory activity, such as compounds **1**, **2**, **4** and **5** shown in (Fig. 1). [13] The SARs of quinoline-based inhibitors suggested that quinoline pharmacophores were responsible for forming hydrogen bonds with the backbone of *c*-Met kinase, and an aryl fragment (B) probably extended into the hydrophobic pocket. Additional hydrogen bonds, which were also crucial for inhibitory activity, are formed by linkers connected phenyl rings A and B.[13–16] By using of Discovery Studio 3.0, the spatial distances of the linkers in compounds **3** (PDB: 3F82), **4** (PDB: 2RFN) and **5** (PDB: 3LQ8) were determined according to co-crystal structures bound to *c*-Met kinase as 6.434, 6.549 and 6.327 Å, respectively. The distances probably fitted aryl fragment (B) into the hydrophobic pocket which resulted in excellent inhibition. Since a large number of quinoline-based inhibitors were examined, it was found that whether the structures of linkers were constrained (**3** and **4**) or not (**1**, **2** and **5**), six chemical bonds (shown in Fig. 1) were retained in linkers which could afford proper spatial distances between phenyl ring A and B.

Several investigations have recognized that *N*-acylhydrazone and its mimics, which contained several hydrogen donors and acceptors, were of diverse biologic activity and strong coordination ability. Especially, they were widely used as building blocks in the design of anticancer agents, exemplified by procaspase-3 activator **7**, *c*-Met kinase inhibitor **8** and topo II inhibitor **9** (Fig. 2).[17–19] Accordingly, we designed a series of N^1-(3-fluoro-4-(6,7-disubstituted-quinolin-4-yloxy) phenyl)-N^4-arylidenesemicarbazide derivatives by molecular hybrid of the 4-phenoxy-6,7-disubstituted quinoline cores and *N*-acylhydrazone scaffolds in which six chemical bonds were reserved in the linkers and the spatial distance,

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http://dx.doi.org/10.1016/j.bmc.2013.06.026

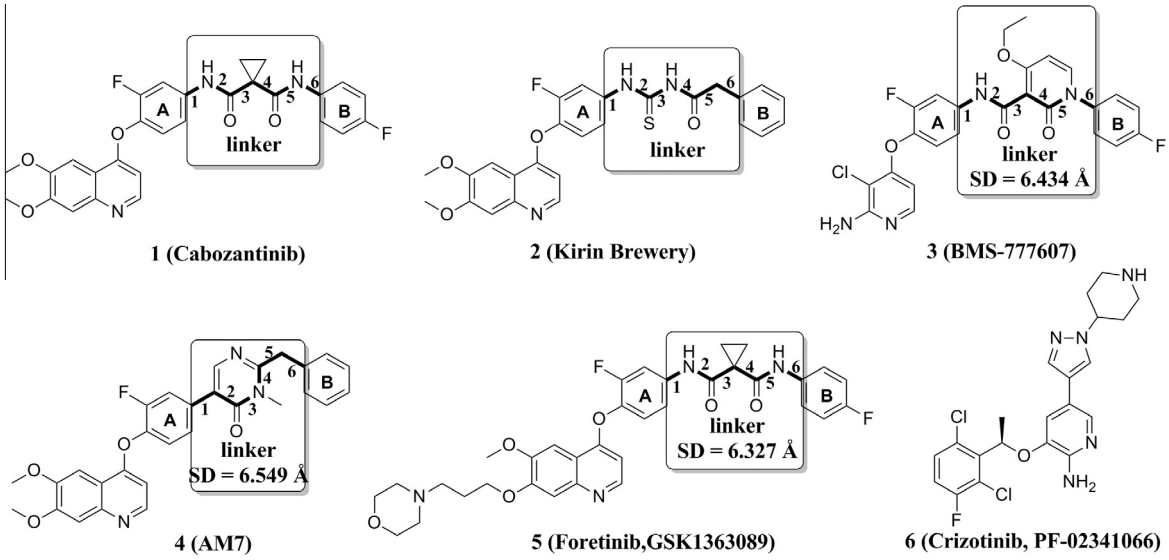

Fig. 1. The representative small-molecule *c*-Met kinase inhibitors.

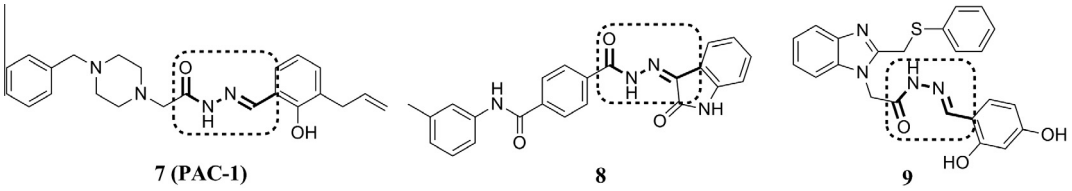

Fig. 2. Anticancer agents bearing *N*-acylhydrazone fragments.

approximate 6.422 Å (determined by Discovery Studio 3.0), was similar to that of **3**, **4** and **5**. In addition, at the 7-position of quinolines, a three-carbon tether which contained different cyclic tertiary amines were introduced as polar and water-solubilizing fragments. The SARs of the novel quinoline-based derivatives were investigated by modifying cyclic tertiary amines (R_1), the aryl rings (R_2), as well as linkers and the most promising compound **28** was found (Fig. 3).

All target compounds were evaluated for their antiproliferative activity in vitro against three *c*-Met-addicted cancer cells which included A549 (human nonsmall-cell lung cancer cell), HT-29 (human colorectal cancer cell) and MKN-45 (human gastric cancer cell) and a *c*-Met less sensitive MDA-MB-231 (human breast cancer cell) for ruling out off-target effects. Several potent compounds were further evaluated against three other cancer cell lines (U87MG, NCI-H460 and SMMC7721). The enzymatic assays were performed in order to determine *c*-Met kinase inhibition and detail the SARs and most of them showed promising inhibition. With Foretinib and PAC-1 as references, the inhibitory activity expressed as IC_{50} are summarized in Tables 1–3.

2. Chemistry

Compounds **20a–e**, **21a–c**, **22a–c**, **23a–c** and **24–42** were synthesized according to the routes outlined in Scheme 1. Commercially available 4-hydroxy-3-methoxyacetophenone was alkylated with 1-bromo-3- chloropropane in the presence of K_2CO_3 to provide **10**.[20] Nearly regioselective nitration with fuming nitric acid,[21] subsequent aminomethylenation by means of modified Vilsmeier–Haack reagent *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) afforded **12**.[22] The intramolecular cyclization in the presence of iron powder and acetic acid afforded the quinolinol core **13**, which underwent a nucleophilic substitution with different amines (morpholine, piperidine, 4-methylpiperidine and pyrrolidine) to

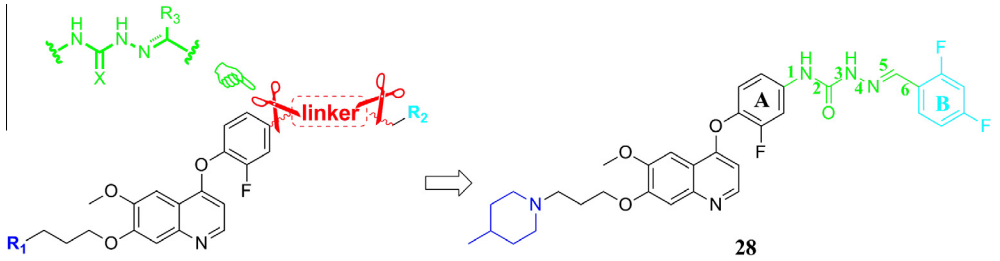

Fig. 3. The design of compound **28**.