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Discovery of novel 2-substituted-4-phenoxypyridine derivatives as potential antitumor agents

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ABSTRACT

A series of 2-substituted-4-phenoxypyridine derivatives were designed, synthesized, and evaluated for their antiproliferative activity against 4 cancer cell lines (A549, HT-29, H460, and U87MG) *in vitro*. Most compounds showed moderate to excellent potency. Nine tyrosine kinases (c-Met, Flt-3, ALK, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, c-Kit, and EGFR) were used to evaluate the inhibitory activities with the most promising analogue **39**, which showed the Flt-3/c-Met IC_{50} values of 2.18/2.61 nM. Structure-activity relationship studies indicated that n-Pr served as R^1 group showed a higher preference, and stronger mono-EWGs on the phenyl ring (such as R^2 = 4-F) was benefited to the potency.

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Cancer is one of the leading causes of morbidity and mortality worldwide, which is the second leading cause of death globally. Cancer was responsible for 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths is due to cancer.[1] Despite the efforts to discover and develop small molecule anticancer drugs in the last decades,[2–4] development of new antitumor agents with improved tumor efficiency, selectivity, and safety remains in urgent need.

Recently, significant progress has been made in the development of c-Met kinase inhibitors, resulting in the marketing of cabozantinib (approved on November 2012 by the U.S. FDA for the treatment of patients with progressive metastatic medullary thyroid cancer, **3**, Fig. 1) and more than 10 candidates under clinical trials.[5–7] We had analyzed the structural characteristics of these c-Met kinase inhibitors. The general structure of small-molecule c-Met kinases inhibitors was summarized as illustrated in Fig. 1, which could be divided to moiety A, B, C, and D. Judging from moiety A, many structure types of these derivatives were included, such as substituted quinoline (**1**–**3**), thieno[2,3-*b*]pyridine (**4**), pyrrolo[2,3-*b*]pyridine (**5**), and 2-amino-3-chloropyridine series (**6**).[8–14] However, the main modification of these different series of derivatives was focused on moiety C (a 5-atom linker), which has two obvious structural characteristics. One is the '5 atoms regulation', which means six chemical bonds distance existed between moiety B and moiety D; the other is the 5-atom linker containing hydrogen, oxygen, and nitrogen atoms which could form hydrogen-bond donor or acceptor.

In our previous study, we introduced 2-oxo-4-chloro-1,2-dihydroquinoline and pyridine fragments into the 5-atom linker based on the two structural characteristics, and the resulting 6,7-disubstitutedquinoline (**7**, Fig. 2) and pyrrolo[2,3-*b*]pyridine derivatives (**8**) showed excellent potency, respectively.[15,16] 1,8-Naphthyridinone fragment was widely used as a building block in the design of anticancer agents. For example, compounds **9** displayed a multitude of biological activities.[17]

In this work, 1,8-naphthyridinone was introduced to the 5-atom linker as illustrated in Fig. 3, because the carbonyl oxygen or two nitrogen atoms in 1,8-naphthyridinone as the hydrogen-bond acceptor have high ability to form hydrogen-bonding interactions with c-Met. 2-substitutedpyridine was used as moiety A. Substituted phenyl ring was reserved as moiety B and moiety D. Small substituents R^1 and R^2 were introduced to investigate their effects on activity of the target compounds. Accordingly, we designed a novel series of 2-substituted-4-phenoxypyridine derivatives bearing the 1,8-naphthyridinone fragment.

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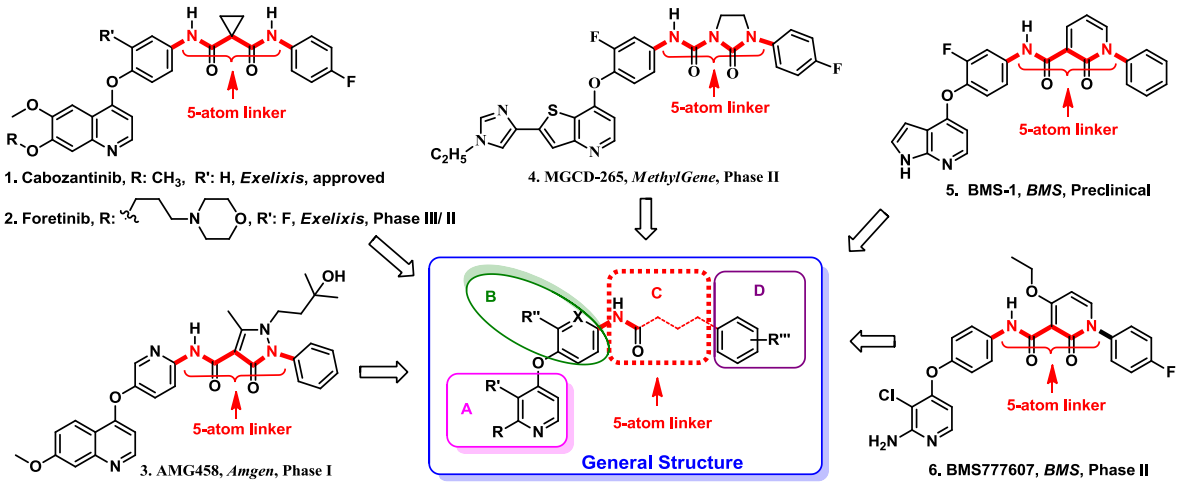

Fig. 1. The representative small-molecule c-Met kinase inhibitors and the summarized General Structure.

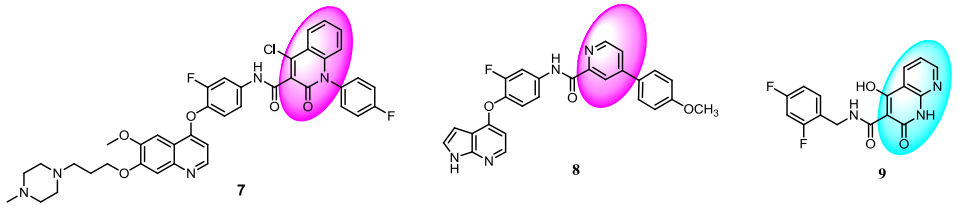

Fig. 2. Antiproliferative agents bearing 2-oxo-4-chloro-1,2-dihydroquinoline (**7**) and pyridine (**8**) in our previous work; potent drug bearing 1,8-naphthyridinone fragment (**9**).

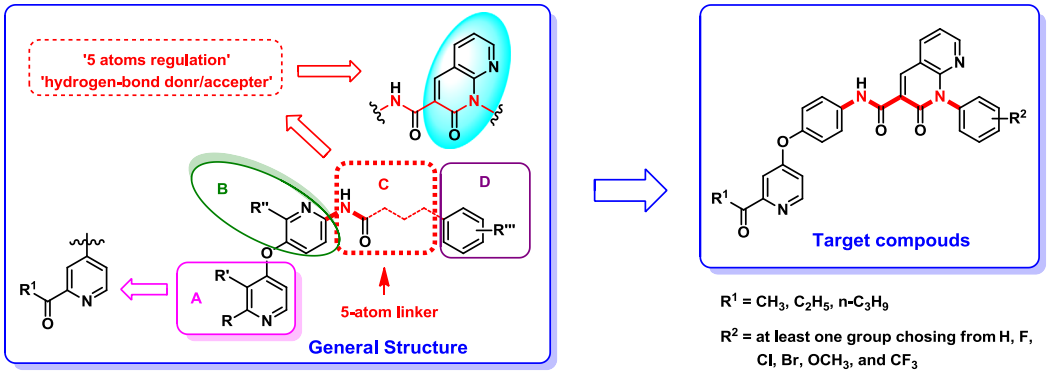

Fig. 3. Design strategy for the 2-substituted-4-phenoxypyridine derivatives bearing 1,8-naphthyridinone fragment.

The antiproliferative effect of the target compounds **19**–**45** were evaluated on the growth of four cell lines *in vitro*,[18,19] namely human lung adenocarcinoma (A549), human colon cancer (HT-29), human lung cancer (H460), and human glioblastoma (U87MG). A549, HT-29, MKN-45, and U87MG are all high expressing cell lines of c-Met kinase.[18,20] There is no overexpression of c-Met in H460 cell line, we chose it to investigate whether these compounds showed potent antiproliferative against the cell line. Moderate to excellent growth inhibition was observed for most of the compounds, and 11 of these compounds were more potent than foretinib against one or more cell lines. Furthermore, seven compounds were chosen for further evaluation of c-Met kinase inhibitory activity *in vitro*. To examine the selectivity, compound **39** was chosen to screen against 8 other tyrosine kinases. To further elucidate the binding mode of these 2-substituted-4-phenoxypyridine derivatives, docking analysis was performed using compound **39**.

The key intermediates 4-(4-amino-2-substitutedphenoxy)-*N*-substituted picolinamide **12a**–**c** were prepared as illustrated in Scheme 1. Catalyzed by NaBr, chlorination of the commercially available 2-picolinic acid with thionyl chloride resulted in the intermediate **10**. Acylation of acyl chloride **10** with amines (methylamine, ethylamine, and propanamine) in the presence of Et_3N proceeded smoothly to yield **11a**–**c**. Etherification of 4-aminophenol with **11a**–**c** catalyzed by potassium *t*-butoxide to give the key intermediates **12a**–**c**.

The target compounds **19**–**45** were prepared as illustrated in Scheme 2. Condensation of substituted aniline with 2-chloronicotinic acid in AcOH at 100 °C resulted in high yield of intermediates **13a**–**i** as white solids. **13a**–**i** were reduced by $LiAlH_4$ in THF to

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