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Research paper

Discovery of novel pyrrolo-pyridine/pyrimidine derivatives bearing pyridazinone moiety as c-Met kinase inhibitors

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ABSTRACT

In continue to our previous research, eight series of pyrrolo[2,3-*b*]pyridine and pyrrolo[2,3-*d*]pyrimidine derivatives bearing pyridazinone moiety were designed, synthesized, and the *in vitro* antitumor activity was evaluated against four cancer cell lines (A549, HepG2, MCF-7 and PC-3). Some selected compounds (**22f**, **22g**, **26c** and **26e**) were evaluated for the activity against c-Met kinase, and according to the results of kinase inhibitory activity, the compound **22g** was further evaluated for other four tyrosine kinases (Flt-3, VEGFR-2, c-Kit and EGFR) to test the enzyme-based selectivity. The most promising compound **22g** showed excellent activity than lead compound Foretinib against A549, HepG2, MCF-7 and PC-3 cell lines, with the IC_{50} values of 2.19 ± 0.45 μM, 1.32 ± 0.26 μM, 6.27 ± 1.04 μM and 4.63 ± 0.83 μM. The structure −activity relationships (SARs) and docking studies indicated that the pyrrolo[2,3-*b*]pyridine derivatives bearing 4-oxo-pyridazinone moiety was superior to the pyrrolo[2,3-*d*]pyrimidine derivatives bearing 6-oxo-pyridazinone moiety. What's more, the target compounds modified with X and Y (X = H, Y = H) were favorable to the activity. And electron drawing groups (EWGs) of 4-Cl-3CF_3 on the aryl group show the best activity.

1. Introduction

c-Met inhibitors, a class of small molecules which can inhibit the enzymatic activity of the c-Met kinase and have therapeutic application in the treatment of various types of cancers [1]. Cabozantinib, the first small molecule c-Met inhibitor, was approved by FDA on November 29, 2012. In recent years, many Cabozantinib derivatives were reported, such as Foretinib, compounds **3** and **4** (The structures are shown in Fig. 1 [2–4]).

Many researches showed that nearly all of the Cabozantinib derivatives show excellent activity and contain a 5-atom linker between the aminophenoxy at C-4 position of quinoline and aryl group, which we called '5-atom regulation'. The '5-atom regulation' have two obvious structural characteristics. The first one is that there is six chemical bonds distance between aminophenoxy at C-4 position of quinoline moiety and aryl group moiety, and the other one is that this "six chemical bonds linker" contains hydrogen, oxygen, and nitrogen atoms which could form hydrogen-bond donor or acceptor (Fig. 1). [5].

In our previous research, several series of pyrrolo[2,3-*b*]pyridine derivatives (compounds **5** and **6**, Fig. 1) were designed and synthesized as potent c-Met inhibitors according to the '5 atom regulation' [6,7]. Most of these compounds exhibited potent activity, especially the most promising compound **6** with the IC_{50} values in the nanomole level. The SARs and docking study exhibited that pyrrolo[2,3-*b*]pyridine moiety and 6-oxo-pyridazinone moiety may be benefit to the *in vitro* activity.

From the 3D model of Foretinib (Fig. 2), we can know that Foretinib contain an intramolecular hydrogen bond (distance = 1.64 A^o) in the 5 atom linker. And inspired by compound 6, further modification was concentrated on pyrrolo[2,3-*b*]pyridine and the 5-atom linker moiety. According to the inspiration from the Foretinib and compound 6, we retained the feature of intramolecular hydrogen bond and the pyrrolo[2,3-*b*]pyridine moiety. Then 4-oxo-pyridazinone was introduced into 5 atom linker moiety to limit the conformation deeply, and then modified

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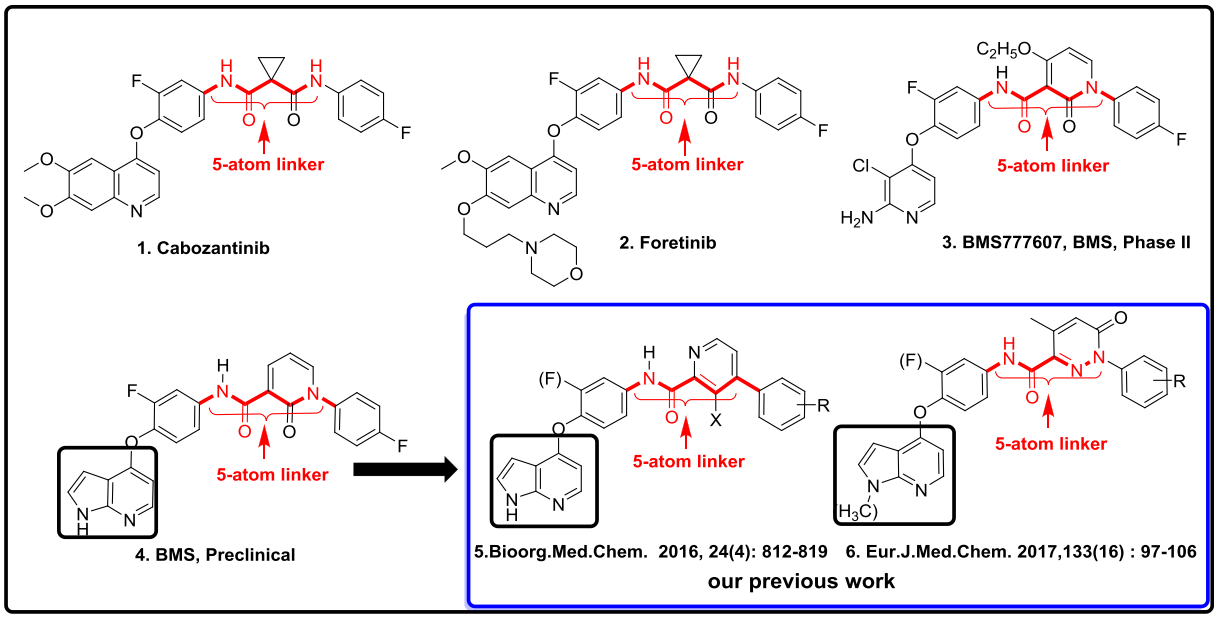

Fig. 1. Structures of small-molecule c-Met inhibitors.

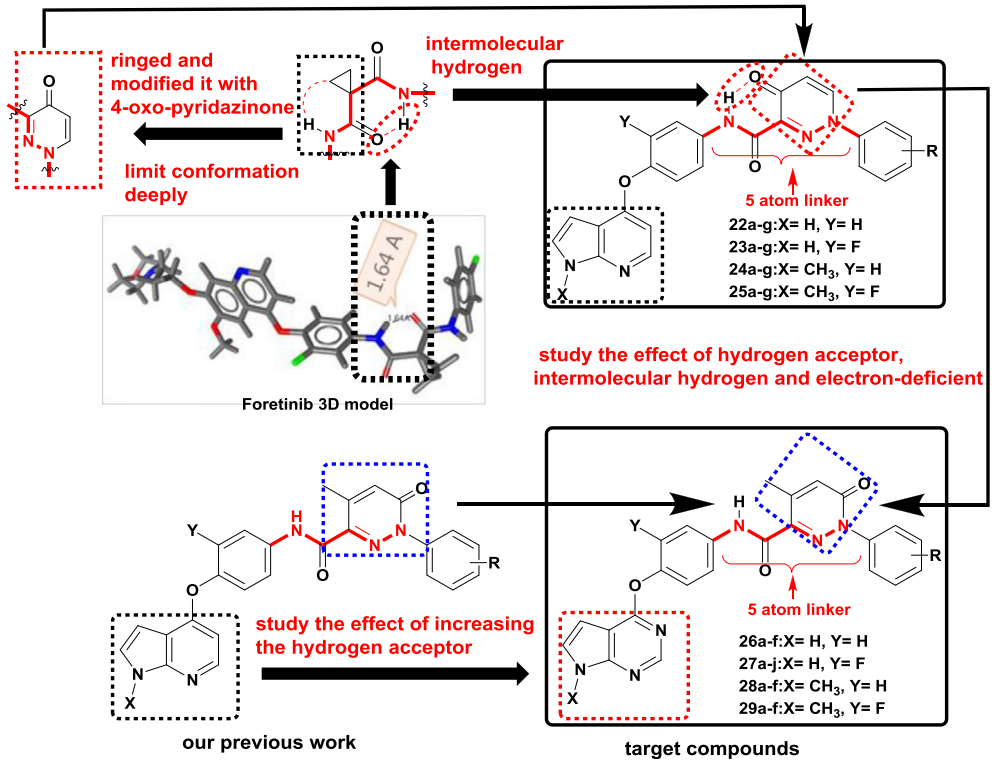

Fig. 2. Structures and design strategy for target compounds **22a-g**, **23a-g**, **24a-g**, **25a-g**, **26a-f**, **27a-f**, **28a-f** and **29a-f**.

with X (X = H\F), Y (Y = H\F) and R to get the first four series compounds (**22a-g**, **23a-g**, **24a-g** and **25a-g**). Furthermore, in order to investigate the effect of hydrogen acceptor and electron-deficient to the target compounds, the pyrrolo[2,3-*b*]pyridine moiety and 4-oxo-pyridazinone moiety were replaced by the pyrrolo[2,3-*d*]pyrimidine and 6-oxo-pyridazinone, respectively. As a result, the compounds **26a-f**, **27a-f**, **28a-f** and **29a-f** were designed.

Herein we disclosed the synthesis and antitumor activity of pyrrolo-pyridine/pyrimidine derivatives bearing pyridazinone moiety against A549 (human lung cancer), HepG2 (human liver cancer), MCF-7 (human breast cancer), PC-3 (human prostate cancer) cancer cell lines, and c-Met kinase. Moreover, AO single staining, AnnexinV/PI staining, enzyme-based selectivity and docking studies were presented in this paper as well.