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Design, synthesis and biological evaluation of c-Met kinase inhibitors bearing 2-oxo-1,2-dihydroquinoline scaffold

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ABSTRACT

A series of 2-oxo-1,2-dihydroquinoline-containing c-Met inhibitors were designed, synthesized and evaluated for their in vitro activities targeting c-Met. Most compounds showed high potency against c-Met with IC_{50} values in the single-digit nM range. Among these compounds, two target compounds, namely **1h** and **1n**, stood out as the most potent c-Met inhibitors with IC_{50}s of 0.6 and 0.7 nM, respectively. And **1a** exhibited higher potency than **BMS-777607** did with respect to the inhibition of cell proliferation. The introduction of electron-donating substituent was favorable for the activities of the compounds to some extent. Furthermore, molecular docking studies also gave encouraging results that supported this work.

c-Met is a prototype member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs). The physiological functions of the c-Met pathway are restricted to mammalian development and tissue homeostasis. Abnormal activation of c-Met has been reported in many types of cancers, occurring as a consequence of gene amplification or rearrangement, transcriptional regulation, as well as autocrine or paracrine ligand stimulation. Importantly, deregulated c-Met activation has been associated with poor clinical outcomes.[1,2] In addition; c-Met signaling is responsible for the resistance acquisition of approved therapies.[3,4] Thus, c-Met axis has emerged as a favorable target for cancer therapy research.

To date, a respectable number of c-Met inhibitors have already been reported and some of them are launched or in clinical trials (Fig. 1)[2,5–11] Literature reported c-Met inhibitor **BMS-777607** (Fig. 2a) showed very potent c-Met inhibition activity.[12] An X-ray crystal structure of **BMS-777607** complexed to the Met kinase domain (Fig. 2b) discloses the mode bound to Met kinase domain.[12] The pyridine nitrogen accepts a hydrogen bond with the backbone NH of Met 1160, while the 2-amino group donates a hydrogen bond to the backbone carbonyl of Met1160. The central phenyl ring forms π–π stacking with Phe1223. The carbonyl of pyridin-2-one accepts a hydrogen bond with the backbone NH of Asp1222. The terminal phenyl ring occupies a deep hydrophobic pocket consisted of Phe1134, Leu1195, and Phe1200.

In view of the mode bound to Met kinase domain, we found that the right side of pyridin-2(1*H*)-one in **BMS-777607** was spacious. So we combined a benzene ring to the pyridin-2(1*H*)-one motif and designed a series of 2-oxo-1,2-dihydroquinoline-containing new c-Met inhibitors (Fig. 2c). Herein we report the synthesis, structural optimization and pharmacological evaluation of the designed compounds **1a**–**t** as c-Met inhibitors.

Compounds **1a**–**t** was prepared from commercially available 2-nitrobenzaldehyde. The synthesis of compounds **1a**–**t** is outlined in Scheme 1. Knoevenagel condensation of 2-nitrobenzaldehyde with ethyl malonate gave **2**, followed by reduction of the nitro group to afford **3**. Then C–N coupling of **3** with substituted phenylboronic acid obtained **4a**–**t**, which was subjected to hydrolysis to provide intermediates **5a**–**t**. 4-(4-Amino-2-fluorophenoxy)-3-chloropicolinamide prepared by using the commercially available 3,4-dichloropyridine[12] was condensed with **5a**–**t** respectively to afford **6a**–**t**. Finally, a Hoffman rearrangement resulted in target compounds **1a**–**t** in 60–82% yields.

The first designed compounds **1a** and **1b** were assayed with the enzymatic activities against c-Met. As expected, **1a** and **1b** showed high potency with an IC_{50} value of 1.8 nM and 9.5 nM, which indicated the benzene-fused strategy was feasible. Compound **1a** displayed proliferative inhibition against EBC-1 cell with an IC_{50} of 67.8 nM while the IC_{50} of **1b** with a *p*-fluoro substituent on the phenyl ring A was more than 1000 nM.

Encouraged by these initial results, we explored the effects of various substituents at phenyl ring A on the inhibitory activity. As illustrated in Table 1, most of the designed compounds showed excellent inhibition against the c-Met enzyme. The inhibitory

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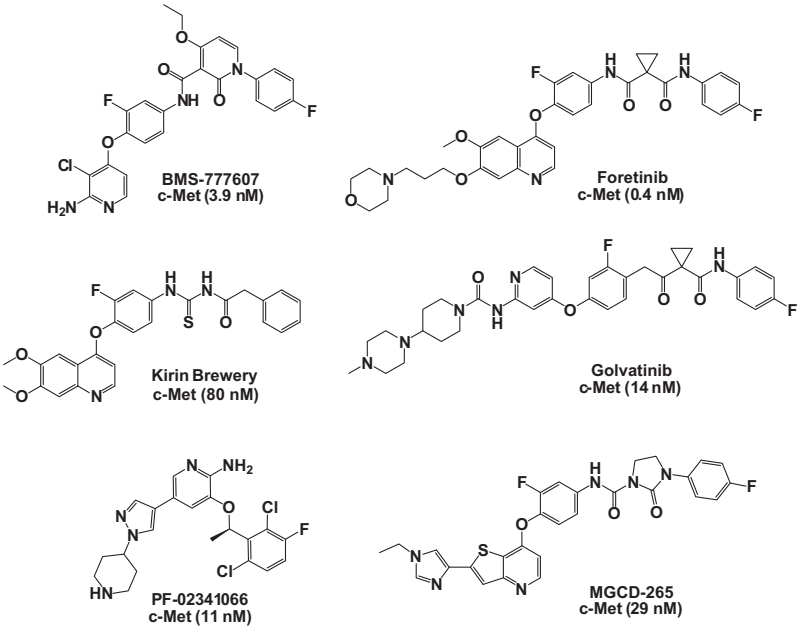


Figure 1. Some representative c-Met inhibitors and their structural characteristics.

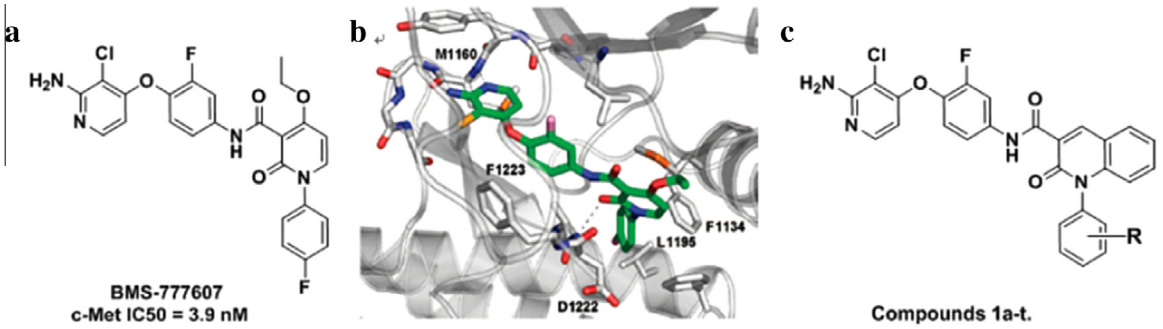
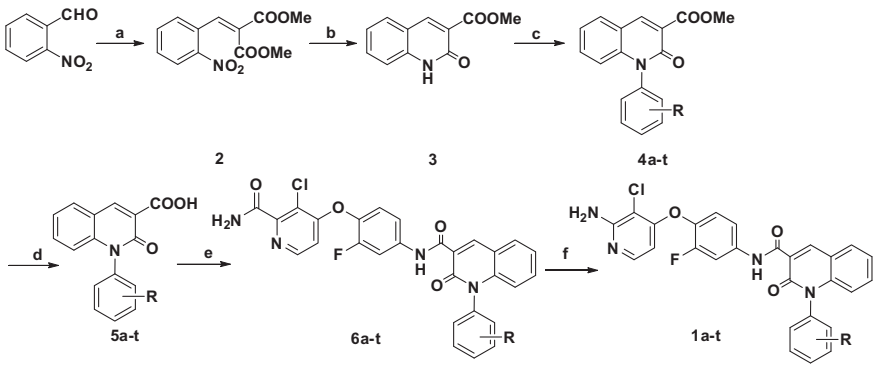


Figure 2. (a) **BMS-777607**, (b) crystal structure of **BMS-777607** bound to Met kinase domain, (c) structure of designed compounds **1a**–**t**.



Scheme 1. Reagents and conditions: (a) potassium carbonate, dimethyl malonate, acetic anhydride, 4 h, 80 °C, 88%; (b) H_2–Pd/C, MeOH, overnight, 96%; (c) substituted phenylboronic acid, CH_2Cl_2, $Cu(OAc)_2$, TEA, molecular sieve, rt, 24 h, 60–82%; (d) KOH, MeOH, reflux, quantitative; (e) (i) sulfuryl dichloride, toluene, reflux; (ii) 4-(4-amino-2-fluorophenoxy)-3-chloropicolinamide, DIPEA, THF, 0 °C–rt, 55–78%; (f) $PhI(OAc)_2$, ethyl acetate, CH_3CN, H_2O, rt, 60–82%.

activities of the meta-substituted analogues (**1e**, **1g**, **1i**) increased in the following order: –OMe (**1i**) > –Me (**1g**) > –F (**1b**). The results above indicated that the introduction of electron-donating substituent is favorable for the activities. This phenomenon was also observed in para-substituted compounds. The results suggested that the inhibitory activities may be influenced by the electron cloud density of the ring A. Nevertheless, compounds **1d** and **1e** with chloro substituted were exceptions with IC_{50} values of 132.7 and 1.0 nM, respectively. In the meantime, we discovered that most disubstituted compounds **1j**–**t** were nearly equipotent