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Discovery of potent 1*H*-imidazo[4,5-*b*]pyridine-based c-Met kinase inhibitors via mechanism-directed structural optimization

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ABSTRACT

Starting from our previously identified novel c-Met kinase inhibitors bearing 1*H*-imidazo[4,5-*h*][1,6]naphthyridin-2(3*H*)-one scaffold, a global structural exploration was conducted to furnish an optimal binding motif for further development, directed by the enzyme inhibitory mechanism. First round SAR study picked two imidazonaphthyridinone frameworks with 1,8- and 3,5-disubstitution pattern as class I and class II c-Met kinase inhibitors, respectively. Further structural optimization on type II inhibitors by truncation of the imidazonaphthyridinone core and incorporation of an *N*-phenyl cyclopropane-1,1-dicarboxamide pharmacophore led to the discovery of novel imidazopyridine-based c-Met kinase inhibitors, displaying nanomolar enzyme inhibitory activity and improved Met kinase selectivity. More significantly, the new chemotype c-Met kinase inhibitors effectively inhibited Met phosphorylation and its downstream signaling as well as the proliferation of Met-dependent EBC-1 human lung cancer cells at submicromolar concentrations.

The MET tyrosine kinase is a cell surface receptor for the hepatocyte growth factor (HGF), a pleiotropic cytokine controlling pro-migratory, anti-apoptotic and mitogenic signals.[1–4] Normal activation of c-Met kinase is essential for wound healing and embryonic development.[2] Aberrant c-Met due to specific genetic lesions, including transcriptional upregulation, gene amplification, activating mutations, increased autocrine or paracrine ligand mediated stimulation, occurred in many types of cancers.[5] Importantly, deregulated c-Met activation has been associated with poor clinical outcomes.[6,7] Furthermore, compelling evidence has linked c-Met overactivation to mediating intrinsic or acquired resistance to targeted therapies.[8,9] All of these emphasize c-Met as an attractive target for cancer therapy. Indeed, quite a few c-Met inhibitors are now under clinical investment, which further proved the feasibility of c-Met inhibition method in cancer therapy.

In the past decade, an impressive number of small molecule c-Met inhibitors have been reported,[10–14] which have basically been categorized into two classes based on their structure and binding modes in the c-Met kinase domain.[2,15] Type I inhibitors bind in a U-shaped conformation to the ATP-binding site at the entrance of the kinase pocket and wrap around Met1211, while type II inhibitors bind to c-Met with an extended conformation that stretches from the ATP-binding site (hinge region) to the deep hydrophobic Ile 1145 pocket near the C-helix region. Some representative chemical structures from each class are illustrated in Figure 1. In general, type I inhibitors block c-Met kinase activity with high selectivity against other kinases, whereas a majority of type II molecules are multikinase inhibitors, but expected to be more effective against the mutations of c-Met active site that disrupt the type I binding mode.[16,17]

Recently, we identified a new class of type II c-Met kinase inhibitors with 1,3,5-trisubstituted-1*H*-imidazo[4,5-*h*][1,6]naphthyridin-2(3*H*)-one scaffold (Fig. 2, exemplified by **LXM-22**), by employing drug repurposing and pharmacophore incorporation strategies.[18] The new scaffold inhibitors displayed promising pharmacological property and cellular efficacy, but the inhibitory activity fell in micromolar range. According to the binding mode predicted by molecular modeling,[18] the 1*H*-imidazo[4,5-*h*][1,6]naphthyridin-2(3*H*)-one-based c-Met kinase inhibitor adopts an extended conformation in the ATP-binding pocket of the enzyme with the activation loop in an inactive, DFG-out conformation. However, the heterotricyclic core resides in the middle of the channel between the hinge region and the DFG motif,

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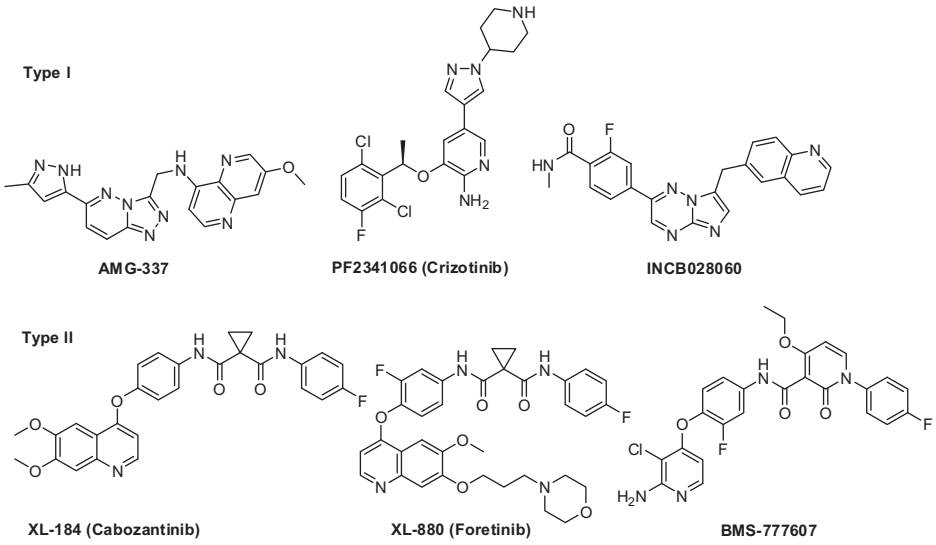

Figure 1. Representative structures of type I and type II c-Met kinase inhibitors launched or under clinical trials.

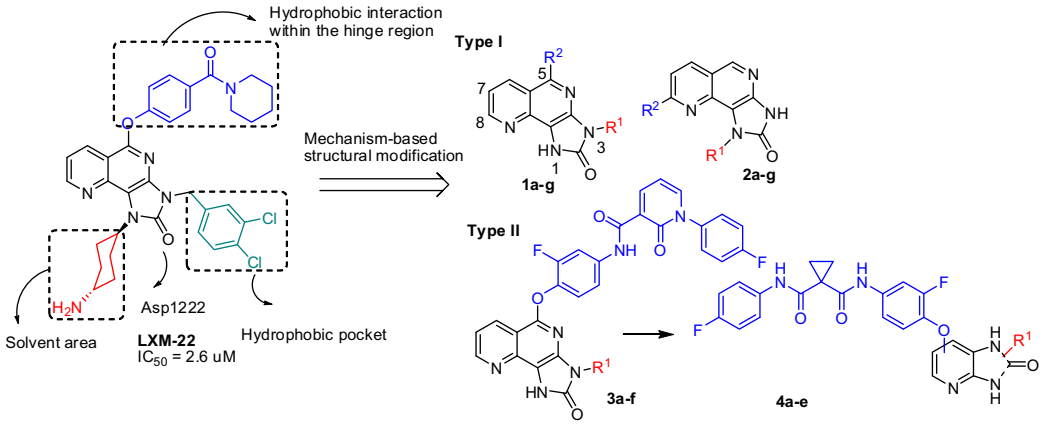

Figure 2. The mechanism-based structural optimization on the 1*H*-imidazo[4,5-*h*][1,6]naphthyridin-2(3*H*)-one scaffold to develop novel type I and II c-Met kinase inhibitors.

due to the bulky size, thus losing the key hydrogen bonding interactions with Met1160. Herein, we tried to improve the potency of imidazonaphthyridinone c-Met inhibitors based on the inhibitory mechanism through two approaches: one is evolved into type I inhibitor by using the 1*H*-imidazo[4,5-*h*][1,6]naphthyridin-2(3*H*)-one as a U-shape inducing moiety with two proper substituents deep into the solvent and hydrophobic regions, respectively (Fig. 2, **1a**–**g**, **2a**–**g**); the other is optimized into a bona fide type II inhibitor by incorporating the typical pharmacophore of N^1-phenyl-N^3-(4-fluorophenyl)malonamide or its bioisostere[19] and further truncation of the core structure to fit the ATP binding site and DFG motif pocket (Fig. 2, **3a**–**f**, **4a**–**e**).

With respect to the U-shaped type I inhibitor design, the optimal substitution pattern was investigated by synthesizing 3,5- and 1,8-disubstituted analogs with hydrophobic and hydrophilic groups incorporated rotationally at the two positions (**1a**–**g**, and **2a**–**g**). As shown in Scheme 1, starting from the 1,6-naphthyridine precursor, which was prepared according to the known procedure,[20] the introduction of the 4-methoxybenzylamino group to 8-position was readily realized by the aromatic nucleophilic substitution of 4-methoxybenzylamine. Then the 1*H*-imidazol-2(3*H*)-one core was constructed in a similar manner as we previously reported,[18] whereby the Curtius rearrangement produced an isocyanate and the following attack of the neighboring 8-amino group furnished the cyclic urea **6**. However, the approach to install the 3-substituent was dependent on the structure of the coupling partner. Mitsunobu reaction and nucleophilic substitution reaction were applied for an alcohol and a halide to convert the 1*H*-imidazol-2(3*H*)-one compound **6** into 1,3-disubstituted intermediates **7**(**b**, **d**, **e**) and **7**(**a**, **c**), respectively. Further introduction of 5-substituent was achieved via Williamson etherification reaction between 5-bromo intermediates **7** and the corresponding alcohols to yield **8b**–**e** or Buchwald–Hartwig cross coupling with amines to give **8a**. The removal of the N^1-4-methoxybenzyl group by TFA and TfOH mixture and further demethylation by BBr_3 afforded the designed 3,5-disubstituted 1*H*-imidazo[4,5-*h*][1,6]naphthyridin-2(3*H*)-one derivatives **1a**–**e**. Interestingly, by tuning the ratio of TfOH and TFA ranging from 10% to 50%, selective debenzylation on the N^1-position without impacting N^3-benzyl group was achieved. Notably, when a privileged structure of 1-(2,6-dichloro-3-fluorophenyl)ethoxy group was installed at 5-position, a different synthetic route was employed. The 5-bromo intermediate **7b** was converted into a phenol **10**, followed by Mitsunobu reaction with 1-(2,6-dichloro-3-fluorophenyl)ethanol to generate **1f**–**g**.

As shown in Scheme 2, the 3,5-disubstituted type II inhibitors **3a**–**f** were synthesized similarly, just appending a specified structure of *N*-(3-fluoro-4-(oxyphenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide at 5-position via Williamson