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Novel 5-(benzyloxy)pyridin-2(1*H*)-one derivatives as potent c-Met inhibitors

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ABSTRACT

A series of novel 5-(benzyloxy)pyridin-2(1*H*)-ones were designed, synthesized and biologically evaluated for c-Met inhibition. Various amides and benzoimidazoles at C-3 position were investigated. A potent compound **12b** with a c-Met IC_{50} of 12 nM was identified. This compound exhibited potent inhibition of EBC-1 cell associated with c-Met constitutive activation and showed high selectivity for c-Met than other tested 11 kinases. The binding model **12b** with c-Met was disclosed by docking analysis.

c-Met is a unique member of receptor tyrosine kinase (RTK) expressed in both normal and malignant cells. It is a cell surface receptor for hepatocyte growth factor (HGF), a pleiotropic cytokine that conveys a unique combination of pro-migratory, anti-apoptotic and mitogenic signals.[1] Aberrant c-Met signalling has been identified in various human cancers. Moreover, both c-Met over-expression and *MET* amplification have been associated with poor clinical outcomes of cancers. Of particular note, HGF/c-Met signaling is responsible for resistance to other cancer therapies.[2] Without a doubt, c-Met has become an attractive target for cancer therapy. In the past decade, a plethora of efforts have been devoted to explore the effective means to interrupt the abnormal c-Met pathway. Small molecule inhibitors are an important class of therapeutic techniques targeting c-Met.

To date, a respectable number of c-Met inhibitors have already been reported.[2,3] A well-known compound, crizotinib (Fig. 1B, **1**), developed by scientists at Pfizer displayed c-Met inhibition with a K_i of 2 nM.[4] The cocrystal structure of crizotinib (Fig. 1A) disclosed its aminopyridine formed bidentate hydrogen bonds with the hinge of c-Met, 2,6-dichloro-3-fluorobenzyloxy fragment involved a π–π interaction with activation loop residue Tyr1230 and 4-(1*H*-pyrazol-1-yl)piperidine reached out into the solvent. Xcovery subsequently reported a series of pyridazin-3-amines as c-Met inhibitors,[5a] in which X376 (Fig. 1B, **2**) with a c-Met IC_{50} of 0.69 nM was identified.[5b] Apart from the bidentate hydrogen bonding fashion, a single hydrogen bond interaction with the hinge region of c-Met was also proved effective. For example, 6-benzyloxyquinoline analogue (Fig. 1B, **4**), of which quinoline nitrogen H-bonded with the Met 1160 residue of the hinge region, exhibited c-Met inhibition at 23 nM.[6] Similarly, researchers at Sanofi demonstrated that 6-benzyloxybenzo[*d*]thiazole derivatives (Fig. 1B, **3**) were potent c-Met inhibitors (IC_{50} <100 nM).[7] The remarkable discrepancies of these structures lie in the fragments interactive with the hing region of c-Met.

The less potency of compound **4** than crizotinib and X376 might be ascribed to the quinoline core only providing one hydrogen bond interactive with the hinge of c-Met. On the basis of the pharmacophore model of compound **4**, a novel pyridin-2(1*H*)-one scaffold was designed (Fig. 2). We envisaged that the pyridin-2(1*H*)-one scaffold might deliver bidentate hydrogen bonding with the hinge, in which the carbonyl oxygen can act as a hydrogen bond acceptor and NH as a donor. The bidentate hydrogen bonding might improve the c-Met potency. Meanwhile, the 2,6-dichloro-3-fluorobenzyloxy group was maintained owing to its potential π–π interaction with the residue Tyr 1230. The side chain R was expected to extend to the solvent accessible region. Herein, we disclosed our efforts to synthesis and biological evaluation of the novel 5-(benzyloxy)pyridin-2(1*H*)-one derivatives against c-Met.

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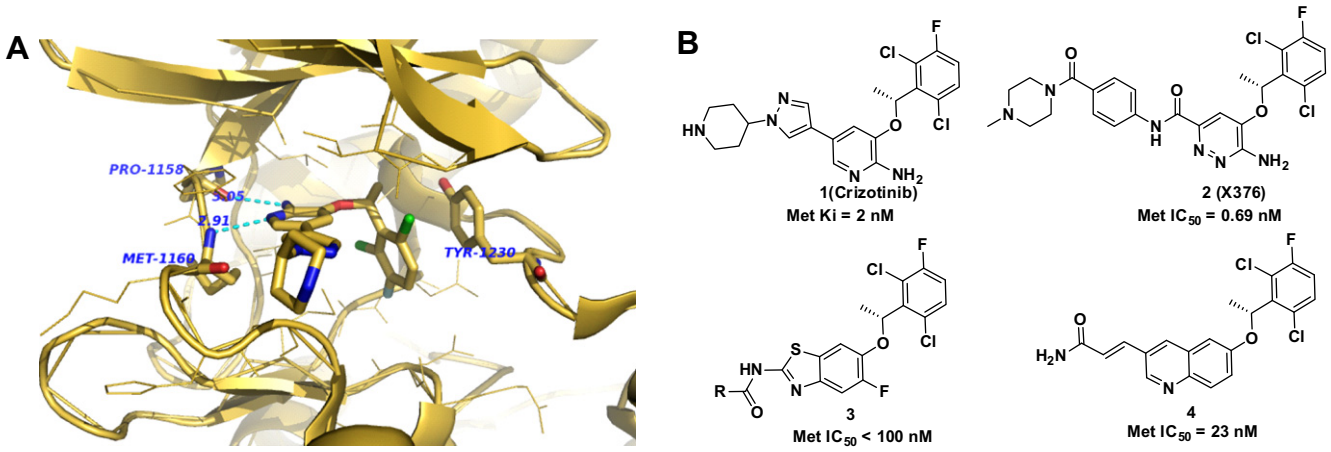


Figure 1. (A) Cocrystal structure of crizotinib bound to c-Met. (B) Selected examples of c-Met kinase inhibitors.

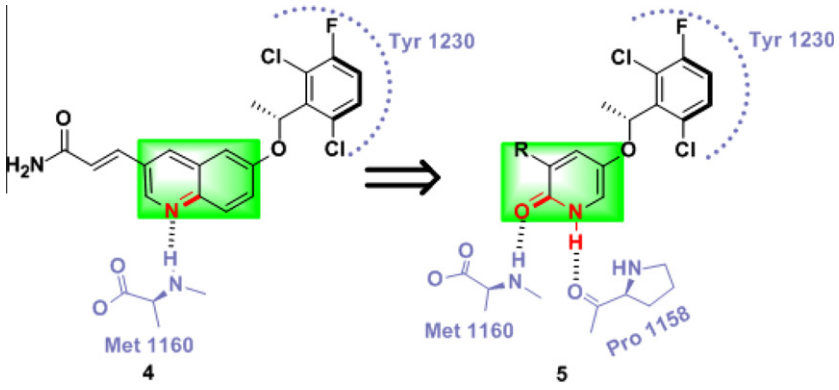
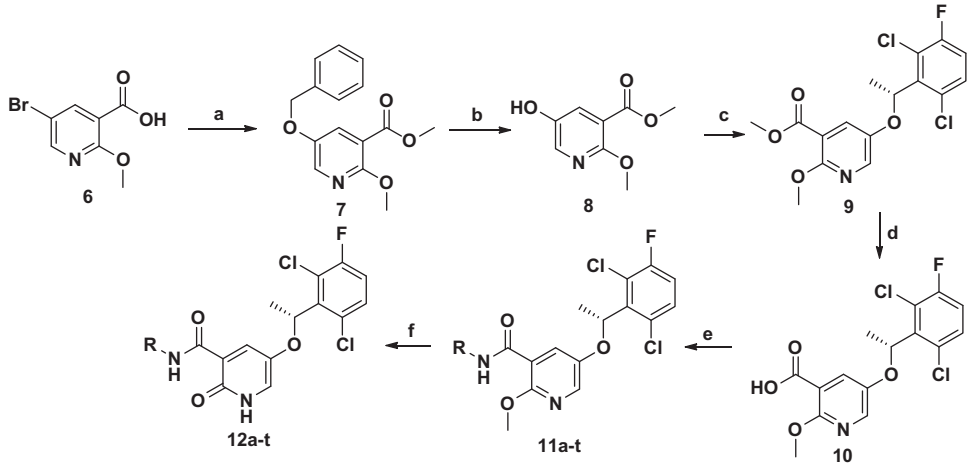


Figure 2. Design of the pyridin-2(1*H*)-one scaffold.



Scheme 1. Reagents and conditions: (a) benzyl alcohol, CuI, 1,10-phenanthroline, Cs_2CO_3, toluene, 110 °C; oxalyl chloride, DMF, CH_2Cl_2, 0–55 °C, MeOH, rt, 43% yield; (b) Pd/C, H_2, MeOH, 91% yield; (c) (*S*)-1-(2,6-dichloro-3-fluorophenyl)ethanol, DIAD, PPh_3, toluene, 0 °C to rt, 85% yield; (d) LiOH, THF/MeOH/H_2O (2/1/1, v/v/v), rt, 95% yield; (e) amines, HATU, DIPEA, DMF, 0 °C to rt, 40–87% yield; (f) TMSCl, NaI, CH_3CN, rt, 46–90% yield.

The construction of 5-(benzyloxy)pyridin-2(1*H*)-one scaffold was described in Scheme 1. According to previous research work,[5a] a series of amide chains were initially installed at C-3 position of the 5-(benzyloxy)pyridin-2(1*H*)-one scaffold. Our synthesis began with commercial available 5-bromo-2-methoxynicotinic acid. C–O coupling of 5-bromo-2-methoxynicotinic acid **6** with benzyl alcohol,[8] followed by esterification of the resulting acid, afforded methyl ester **7** in 43% overall yield. The hydroxyl group was smoothly installed by debenzylation of the intermediate **7**. Treatment of the methyl 5-hydroxy-2-methoxynicotinate **8** with (*S*)-1-(2,6-dichloro-3-fluorophenyl)ethanol under Mitsunobu conditions gave the key intermediate **9** in 85% yield.[9] Hydrolysis of the ester **9** followed by coupling with a series of amines deliver **11a–t** (40–87% yield). Finally, compounds **12a–t** were obtained in