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Multisubstituted quinoxalines and pyrido[2,3-*d*]pyrimidines: Synthesis and SAR study as tyrosine kinase c-Met inhibitors

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ABSTRACT

Two series of new analogues were designed by replacing the quinoline scaffold of our earlier lead **2** (zgwatinib) with quinoxaline and pyrido[2,3-*d*]pyrimidine frameworks. Moderate c-Met inhibitory activity was observed in the quinoxaline series. Among the pyrido[2,3-*d*]pyrimidine series, compounds **13a–c** possessing an O-linkage were inactive, whilst the N-linked analogues **15a–c** retained c-Met inhibitory potency. Highest activity was observed in the 3-nitrobenzyl analog **15b** that showed an IC_{50} value of 6.5 nM. Further structural modifications based on this compound were undergoing.

Similar to most of the receptor tyrosine kinases (RTK), the hepatocyte growth factor (HGF) c-Met is a regulator of many critical cellular processes including embryological development, cell growth, differentiation, neovascularization and tissue regeneration.[1,2] Aberrantly high expression of HGF/c-Met has been implicated in a variety of solid tumors.[3–9] Therefore, c-Met has emerged as an attractive molecular target and inhibition of HGF/c-Met signaling pathway has shown great therapeutic benefit as novel cancer therapy.[10–15] Among the large number of c-Met-targeting small molecules reported recently,[16–18] crizotinib (**1**, PF-02 341066, Fig. 1) has been the only one approved by FDA as a first-in-class c-Met inhibitor antitumor drug. However, this drug is indeed a dual inhibitor with equal potency at both c-Met and ALK (anaplastic lymphoma kinase) kinases.[19] Therefore, a direct correlation between the clinical anti-cancer benefit and the c-Met potency is dampened by the polypharmacy profile, and highly selective and potent c-Met inhibitors are emergently needed as probes to validate clinical efficacy of the c-Met targeting strategy.

We recently reported[20,21] a series of highly potent c-Met inhibitors structurally featured by multisubstituted quinolines. One of these compounds, 3-(4-methylpiperazin-1-yl)-*N*-(3-nitrobenzyl)-7-(trifluoromethyl)quinolin-5-amine (**2**)[20], also named zgwatinib (Fig. 1), displayed high c-Met potency both at enzymatic (0.93 nM) and cellular (230 nM) levels, thereafter was selected for earlier preclinical investigations. Meanwhile, a series of triazolo[4,3-*b*]pyridazine analogues were designed[21] by merging the 3-piperazinyl-7-trifluoromethylquinoline core of **2**[20] and the triazolopyridazine core of **3**,[15] another potent c-Met inhibitor reported by Amgen, into one molecule to improve the memberane permeability and then eradicate the discrepancy between the enzymatic and cellur potency of **2** (Fig. 2). Unfortunately, these new triazolo[4,3-*b*]pyridazin-3-ylmethanamines **4**[21] showed much reduced inhibitory effects to c-Met enzyme.

As a continuation of our study toward the identification of potent c-Met inhibitors, we decided to take advantage of the widely-used quinoxazoline skeleton as a privileged scaffold of RTK inhibitors and modifiy it with the three key substutients of compound **4** or lead **2**, thereby designing a new series of quinoxaline analogues **I** (Fig. 2). Meanwhile, replacement of the quinoline core **2** with a pyrido[2,3-*d*]pyrimidine artwork and concurrent incorporation of the two side chains of **1** led to another series of new analogues **II** (Fig. 2). Herein, in this report we disclose the synthesis and c-Met inhibition study of these two series of new analogues.

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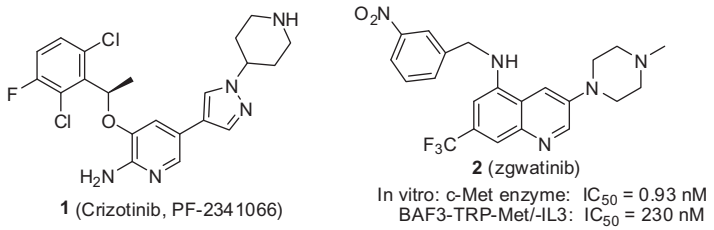


Figure 1. Marketed c-Met inhibitor **1** and our earlier reported compound **2**.

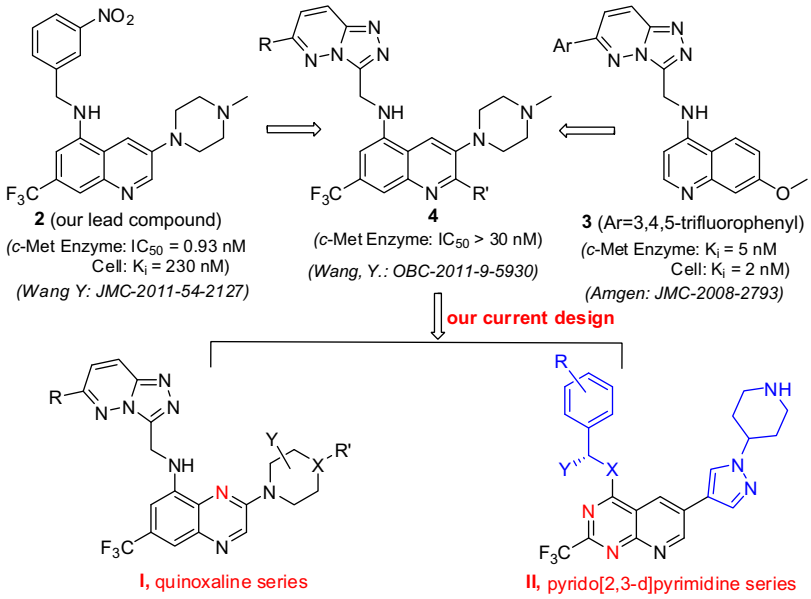
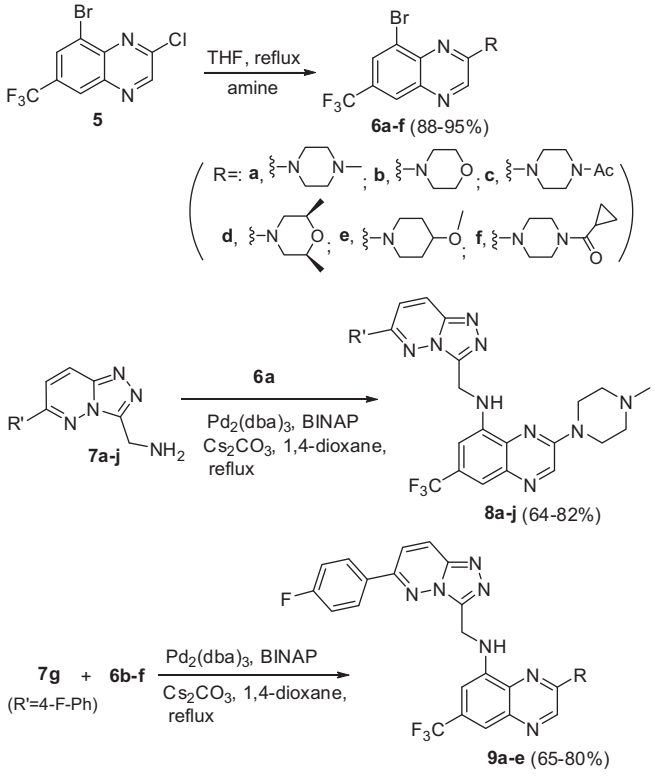


Figure 2. Our new compounds design.



Scheme 1. Synthesis of compounds **8a–j** and **9a–e** (Series **I**).

The synthesis of compound series **I** was started from 3-chloro-5-bromo-7-trifluoromethylquinoxaline (**5**)[22] which was prepared by following a literature procedure. As described in Scheme 1, treatment of **5** with variant amines provided 3-amino-quinoxalines **6a–f** in 88–95% yields. $Pd_2(dba)_3$-catalyzed *C–N* coupling[20] of **6a** with (6-substituted-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methanamines **7a–j** afforded **8a–j** in 64–82% yields. Meanwhile, coupling of 4-fluorophenyl substituted [1,2,4]triazolo[4,3-*b*]pyridazin-3-ylmethanamine **7g** with bromides **6b–f** yielded N-substituted piperazines **9a–e** in 65–80% yields.

Table 1
c-Met activity of compounds **8a–j**[a]

Compd	R′	IC_{50}[a] (nM)
8a	H	2500 ± 67.0
8b	MeO	2700 ± 317
8c	2-Thienyl	659 ± 129
8d	3-Thienyl	441 ± 52.5
8e	2-Furyl	409 ± 183
8f	Ph	1980 ± 328
8g	4-F-Ph	626 ± 97.2
8h	3-F-Ph	385 ± 84.7
8i	3-Cl-Ph	257 ± 40.3
8j	1-Me-pyrazol-4-yl	924 ± 179
2[20]	—	0.93 ± 0.18
4[21]	R=R′=H	330

[a] In vitro kinase assays were performed with the indicated purified recombinant c-Met kinase domains, IC_{50}s were calculated by Logit method from the results of at least three independent tests with six concentrations each.