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Novel Mps1 kinase inhibitors: From purine to pyrrolopyrimidine and quinazoline leads

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ABSTRACT

Mps1, also known as TTK, is a mitotic checkpoint protein kinase that has become a promising new target of cancer research. In an effort to improve the lead-likeness of our recent Mps1 purine lead compounds, a scaffold hopping exercise has been undertaken. Structure-based design, principles of conformational restriction, and subsequent scaffold hopping has led to novel pyrrolopyrimidine and quinazoline Mps1 inhibitors. These new single-digit nanomolar leads provide the basis for developing potent, novel Mps1 inhibitors with improved drug-like properties.

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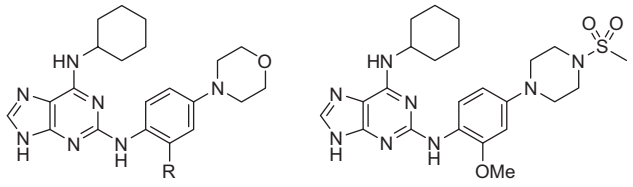
Mps1, also known as TTK, is a dual specificity protein kinase that phosphorylates tyrosine, serine or threonine residues with a critical role during mitosis. Mps1 facilitates chromosomal alignment during metaphase, as well as proper attachment of the bipolar microtubules to the kinetochores by eliminating misattachments.[1,2] It is also required for the full assembly of the spindle checkpoint proteins at the kinetochore and activation of this complex.[3]

Mps1 is dynamic kinase expressed only in proliferating cells and activated via phosphorylation during mitosis. It is over expressed in various human tumors and necessary for cellular proliferation. Mps1 inhibition has been shown to cause premature mitotic exit and gross aneuploidy, which is ultimately associated with cell death. It has been hypothesized that mitotic checkpoints are necessary to sustain cancer cellular proliferation in the presence of aneuploidy. Thus, Mps1 inhibition has become a promising new target of cancer research.

We have recently published our efforts developing purine based lead structures **1a**, **1b** and **2** as potent, selective, novel inhibitors of Mps1 (Fig. 1). Purine **1a** has been shown to disrupt the spindle assembly checkpoint, resulting in chromosome segregation defects and aneuploidy.[4,5] Purine **1a** also demonstrated cytotoxicity across a broad panel of tumor cell lines and exhibited antitumor activity in nude mice bearing human tumor xenografts.[4] Since we initiated our efforts, several promising Mps1 kinase inhibitors have been published (Fig. 2).[6]



1a: R = Me
1b: R = OMe

2

Figure 1. Myrexis Mps1 lead structures.

Due to the high molecular weight (MW) and polar surface area (TPSA) of these leads (Table 1), a de novo design effort was undertaken. Herein we report those efforts leading to new pyrrolopyrimidine and quinazoline inhibitors of Mps1. These new analogs

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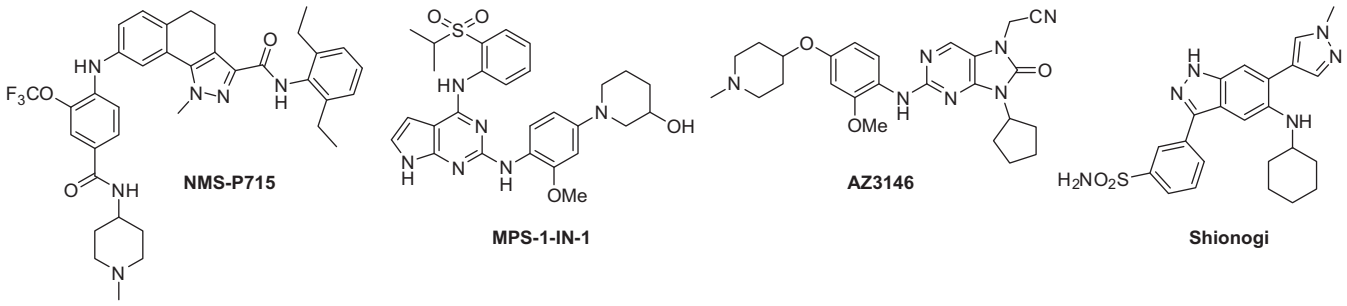
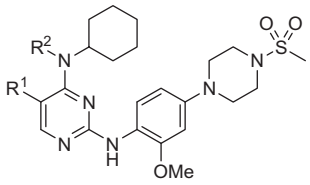


Figure 2. Published Mps1 kinase inhibitors.

Table 1
Structure–activity relationships of pyrimidines



Compd	R^1	R^2	Mps1[a] IC_{50} (nM)	HCT116[a] IC_{50} (μM)	MW	TPSA	LE[b]
1a	—	—	5	0.023	424	100	0.27
2	—	—	2	0.011	501	137	0.25
6	H	H	>100	—	461	108	—
7	H	Me	35	2.0	475	99	0.23
8	Me	H	28	1.5	475	108	0.23
9	Me	Me	>100	—	489	99	—

[a] Values are means of two experiments, standard deviations are ±10%.
[b] LE = −Log(Mps1 IC_{50})/# of heavy atoms.

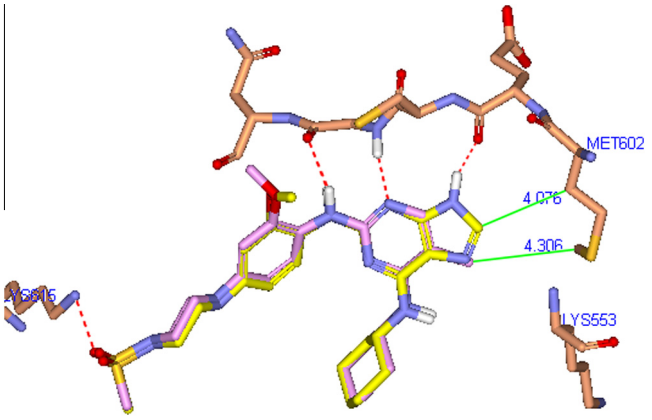
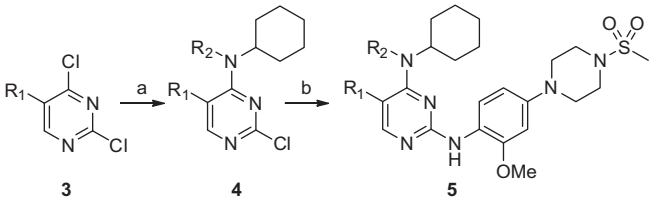


Figure 3. Binding model overlay with 5-methyl pyrimidine structure (pink) and Mps1 lead structure **2**.

demonstrate potent Mps1 activity with significantly reduced TPSA while maintaining their ligand efficiency (LE).[7]

In an effort to reduce the MW and TPSA of the lead compounds, a series of pyrimidines were first designed and modeled. The binding model overlay of the 5-methyl pyrimidine scaffold with purine lead compound **2** is shown in Figure 3.[8]

The synthesis of the diaminopyrimidine inhibitors is shown in Scheme 1.[9] The synthesis begins with commercially available 2,4-dichloropyrimidines **3** (R^1 = H or Me). Heating cyclohexyl amine or *N*-methylcyclohexylamine with **3** and triethylamine in THF at 50 °C provided compound **4** (R^1 = H or Me; (R^2 = H or Me).



Scheme 1. Reagents and conditions: (a) amine, TEA, THF 50 °C; (b) aniline, cat. TsOH, dioxane, 170 °C, MW.

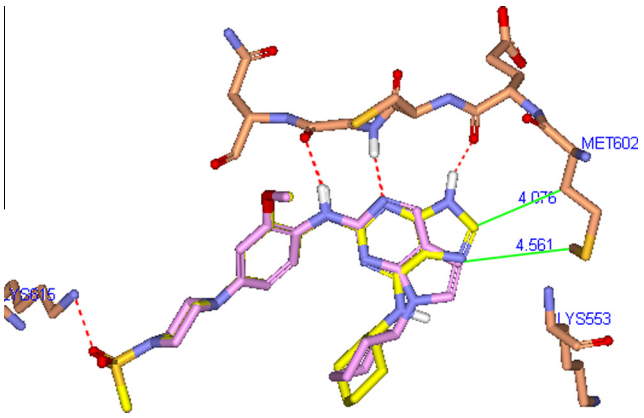


Figure 4. Binding model overlay with *N*-cyclohexyl pyrrolopyrimidine structure (pink) and Mps1 lead structure **2**.

Reaction of **4** with the desired aniline under catalytic acid conditions in the microwave provided the diaminopyrimidines **5**.[10]

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