224 Orally Bioavailable and Brain Penetrant Mps1/TTK inhibitors as cancer therapeutics

Asset Overview

Product Type	Small molecule
Indication	Oncology
Current Stage	Lead Identification/optimization
Target(MoA)	Mps1/TTK inhibitor
Brief Description	Upregulation of the mitotic kinase Mps1/TTK correlates to aggressive phenotypes in both solid and hematological malignancies. Researchers at Ohio State have discovered an orally bioavailable and brain penetrant Mps1/TTK inhibitor that exhibits single agent tumor growth inhibition in a murine xenograft model of human triple-negative breast cancer (TNBC) upon daily administration.
Organization	The Ohio State University

Differentiation

□ **Rationale for Targeting Mps1**

- Mps1 activates the spindle assembly checkpoint to ensure faithful segregation of chromosomes during mitosis
- In the context of the increased chromosomal instability typical of cancer, Mps1 upregulation prevents mitotic catastrophe due to severe aneuploidy
- In cancer, pharmacologic inhibition of Mps1 causes severe defects in chromosomal segregation, resulting in catastrophic levels of aneuploidy
- Importantly, Mps1 inhibition synergizes with microtubule-targeted therapy, presenting clear opportunities for combination therapy

□ **Key Information about Mps1 Inhibitor**

- The lead is designed to provide an advantageous combination of potency and safety to dampen systemic toxicity without sacrificing therapeutic effect
- Tumor-bearing mice dosed daily for six weeks with an efficacious dose of our lead compound exhibited no adverse effects on body weight
- Oral bioavailability in mice was 59% with a brain-to-plasma ratio of 0.2
- Anti-proliferative effect has been demonstrated in vitro on cell lines spanning a number of indications
- In vitro functional assays confirm that our lead compound disrupts the proper functioning of the spindle assembly checkpoint and decreases centriole duplication
- Upcoming preclinical studies are intended to assess PK/PD relationship, efficacy and safety
- In vitro ADME studies and structural characterization of the binding between Mps1 and our lead compound are in progress
- Mps1 expression level, aneuploidy status and/or genetic background may predict sensitivity to our lead compound

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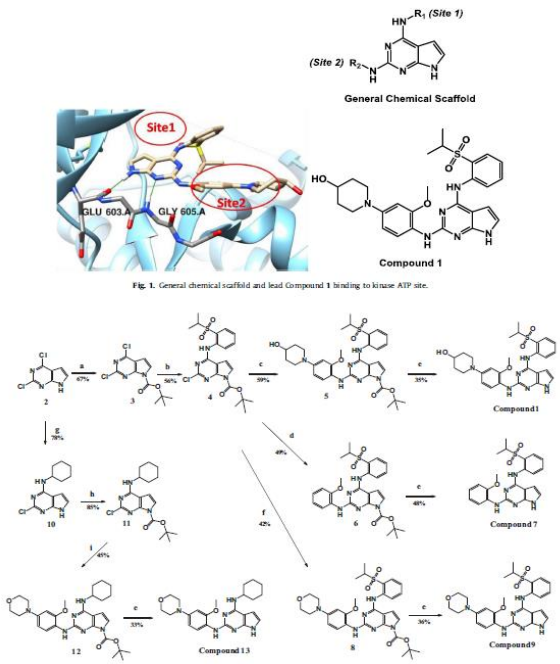
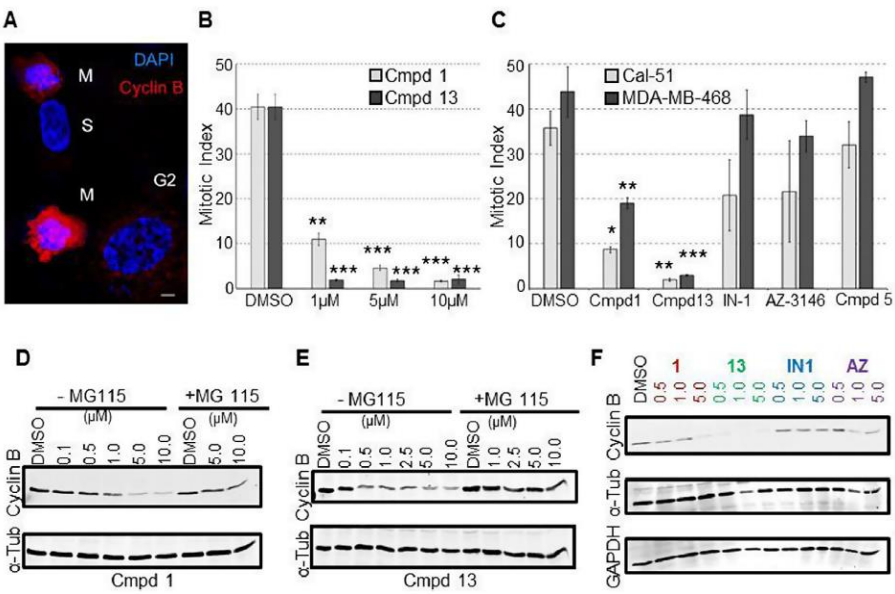
Key Data

Syntheses of Compounds 1, 7, 9 and 13



Reagents and conditions: (a) di-tert-Butyldicarbonate, DMAP, DIEA, DCM, reflux, 15 min. (b) 2-(Isopropylsulfonyl)aniline, Pd2(dba)3, XPhos, K2CO3, t-butanol, 100 C, 4 h. (c) 1-(4-Amino-3-methoxyphenyl-piperidin-4-ol, Pd2(dba)3, XPhos, K2CO3, t-butanol, 100 C, 6 h. (d) 2-Methoxyaniline,Pd2(dba)3, XPhos, K2CO3, t-butanol, 100 C, 4 h. (c) 1-(4-amino-3-methoxyphenyl)-piperidin-4-ol, Pd2(dba)3, XPhos, K2CO3, t-butanol, 100 C, 6 h. (e) TFA, DCM, rt, 4 h. (f) 2-Methoxy-morpholinoaniline, Pd2(dba)3, XPhos, K2CO3, t-butanol, 100 C, 4 h. (g) Cyclohexylamine, TEA, EtOH, reflux, overnight. (h) di-tert-butyldicarbonate, DMAP, DIEA, DCM, reflux, 15 min. (i) 2-methoxy-4-morpholinoaniline, Pd2(dba)3, XPhos, K2CO3, t-butanol, 100 C, 6 h.

Compound 1 and compound 13 attenuate the spindle assembly checkpoint in breast cancer cells



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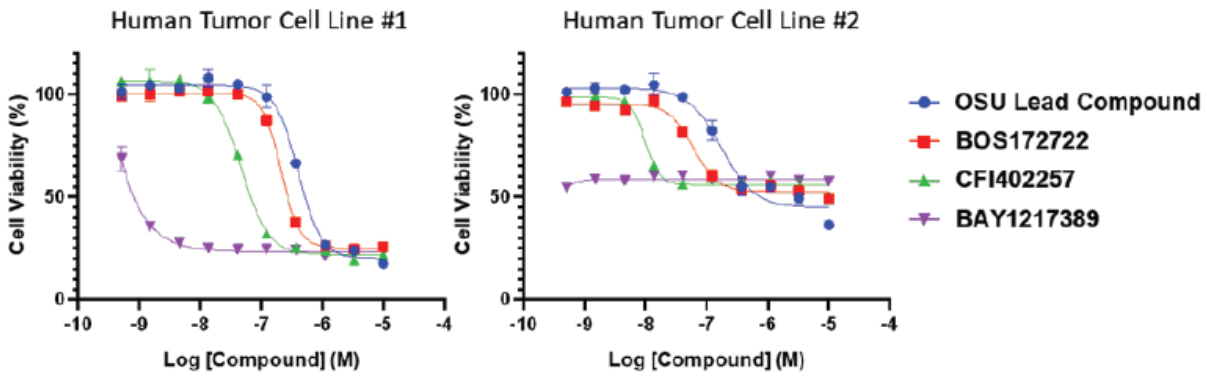
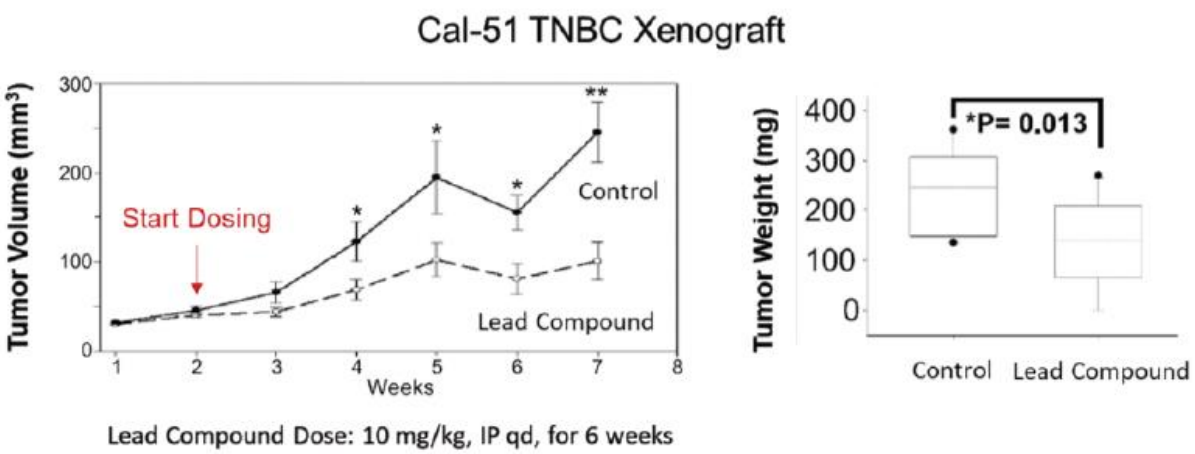
IC50 of Mps1/TTK Inhibitors (small molecule)



Two human tumor cell lines were treated for 72 hours with our lead compound or one of three reported Mps1 inhibitor clinical candidates. Our lead compound shows a similar dose-response profile to the clinical candidates with the expected reduced potency. (Reaction Biology Corp.)

Therapeutic effects of Mps1/TTK Inhibitors (small molecule)



OSU's lead compound attenuates growth of a Cal-51 Triple Negative Breast Cancer (TNBC) xenograft in mice when dosed daily at 10 mg/kg IP for 6 weeks

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Intellectual Property

Patent No.	US 2019-0106422 A1
Application Date	2015.11.05
Status	Application Pending
Country	US

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