TANGO therapeutics™

Discovery of TNG462

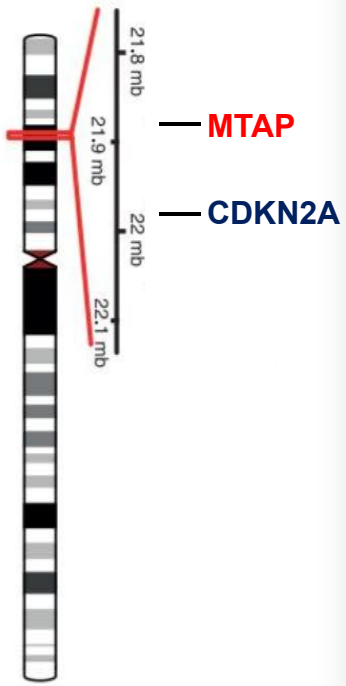
A highly potent and selective MTA-cooperative PRMT5 inhibitor synthetic lethal for MTAP deleted cancers

Kevin Cottrell

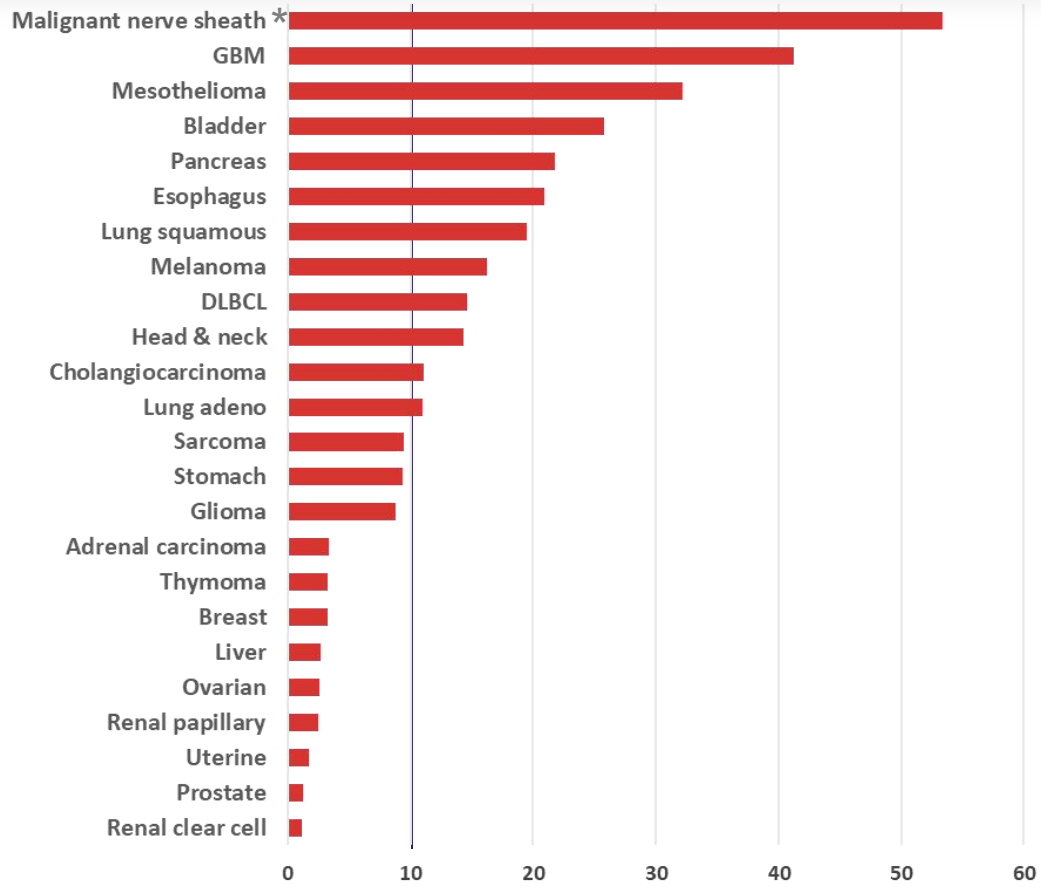
August 16, 2023
ACS National Meeting, San Francisco

PRMT5 provides a large opportunity for treatment of cancer

Chromosome 9



MTAP homozygous deletion frequency



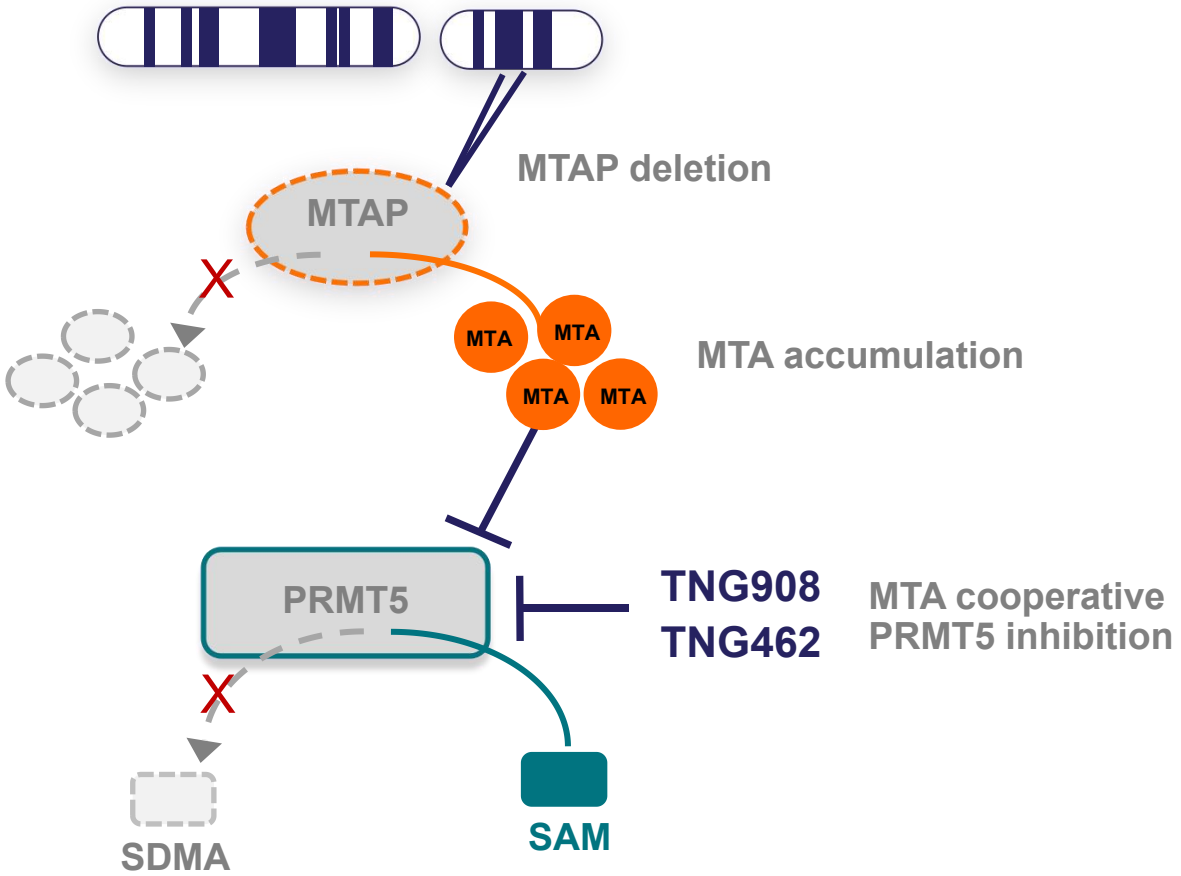
10-15% of all human cancers are MTAP-deleted

- MTAP is co-deleted with CDKN2A
- Clear path to clinical POC in MTAP-null solid tumors
- Potential for histology-agnostic registration

TCGA PanCancer Atlas
*Lee et al, Nature Genetics 2014

PRMT5 and MTAP are a synthetic lethal pair

Cancers with MTAP deletion are more vulnerable to PRMT5 inhibition than normal cells



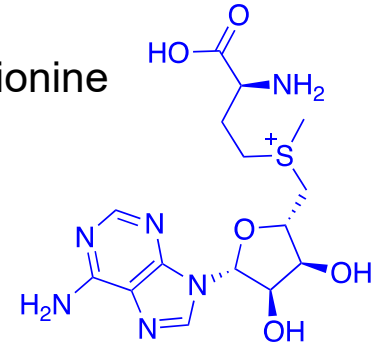
Mechanism of action

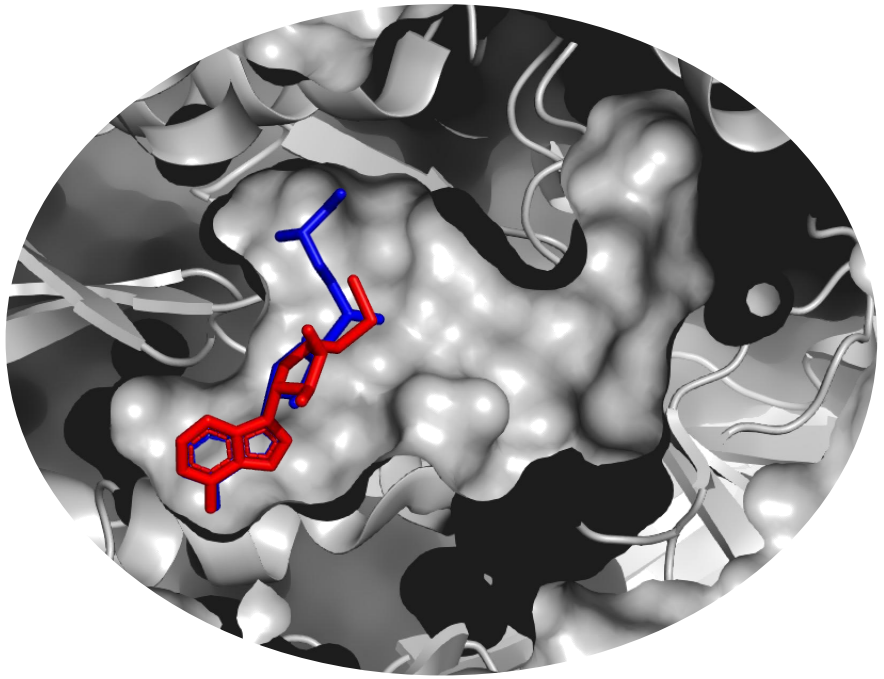
- MTAP deletion causes MTA to accumulate
- MTA binds to and inhibits PRMT5
- MTA-cooperative PRMT5 inhibitors selectively bind to the PRMT5-MTA complex and selectively kill MTAP-deleted cancer cells

Mavrakis et al., Science 2016; Kryukov et al., Science 2016; Marjon et al., Cell Reports 2016

Multiple mechanisms of inhibition available for PRMT5

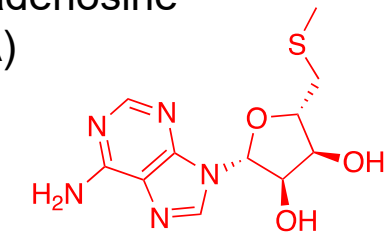
S-adenosylmethionine (SAM)





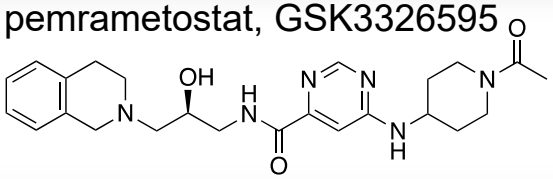
PRMT5 cofactor and substrate binding sites

5'-methylthioadenosine (MTA)



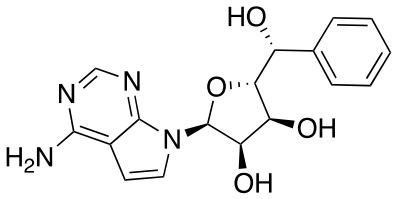
SAM uncompetitive

pemrametostat, GSK3326595



SAM competitive

LLY-283



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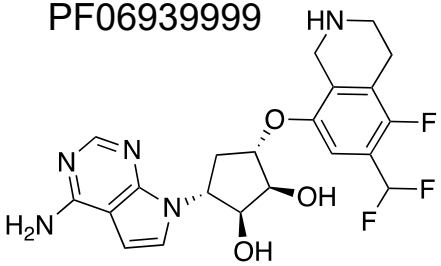

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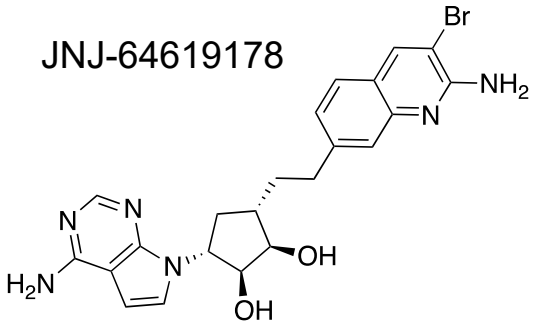
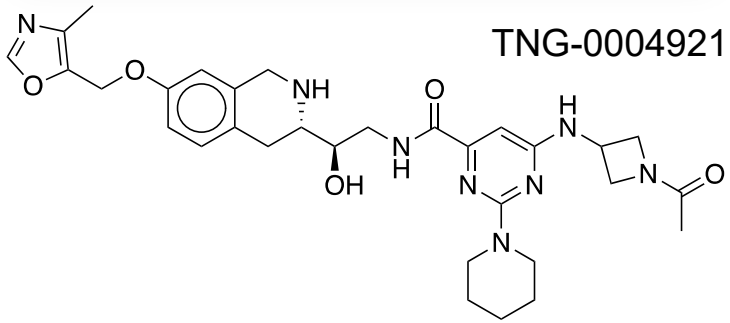


MTA uncompetitive

TNG-0004921



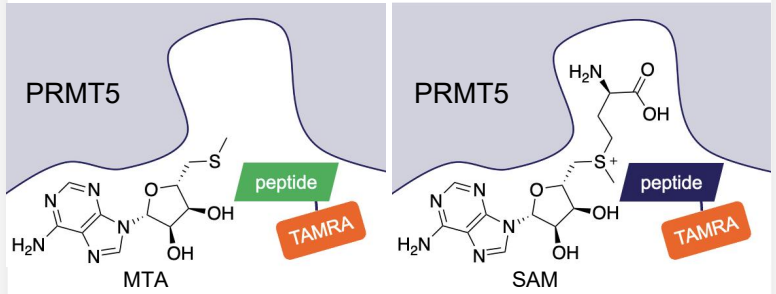
	MTAP del	MTAP WT
Cellular biomarker IC_{50} (μM)	0.093	4.37
Cellular viability GI_{50} (μM)	3.48	> 20

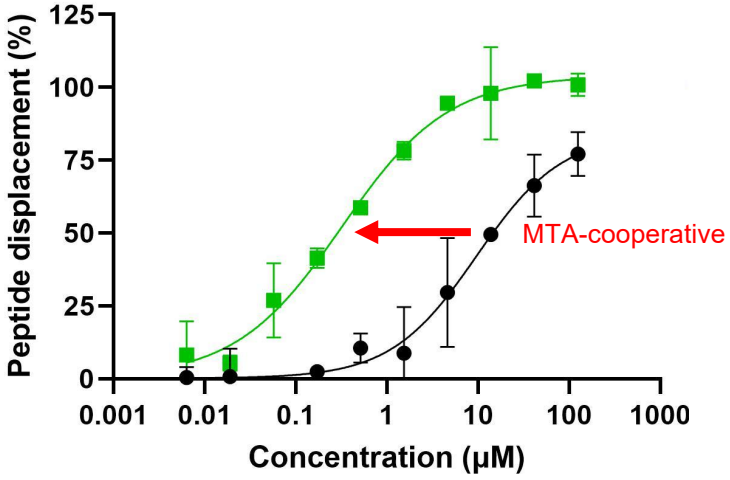
WO2021086879 (6 May 2021)

Assays to measure biochemical and cellular selectivity

Biochemical

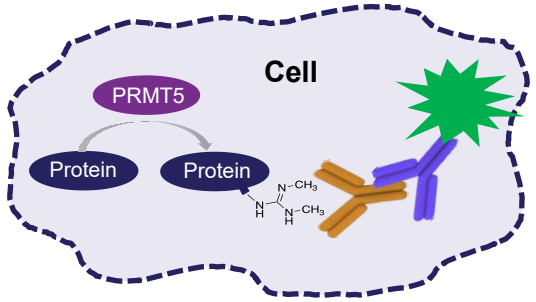
Fluorescence polarization displacement of TAMRA-labeled peptide

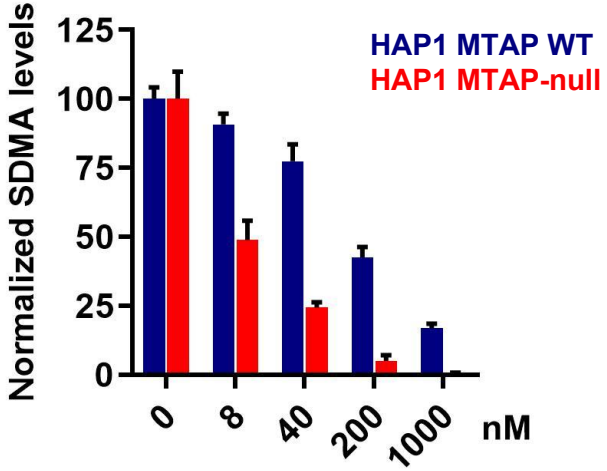




Cellular PD

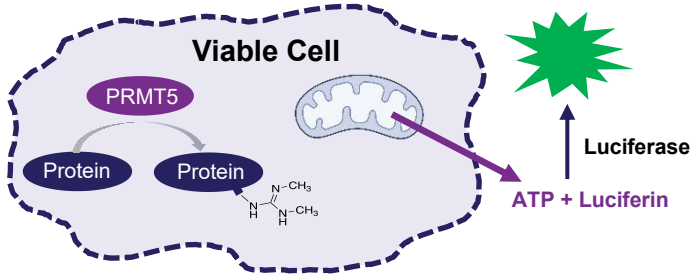
In-Cell Western detection of SDMA (symmetric dimethylarginine) in HAP1 MTAP isogenic cell lines

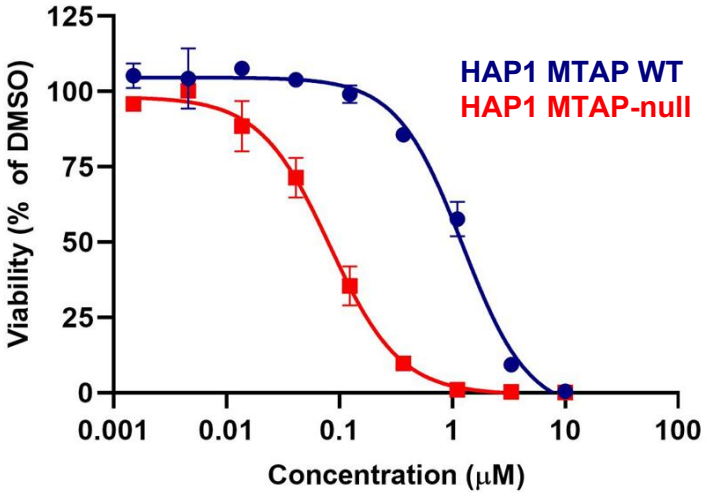




Cellular viability

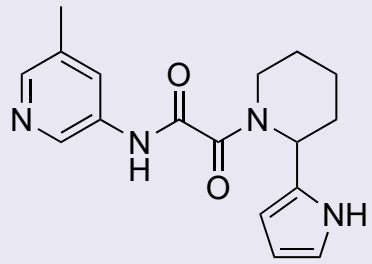
7-day viability assay assessed by CellTiter-Glo in HAP1 MTAP-isogenic cell lines





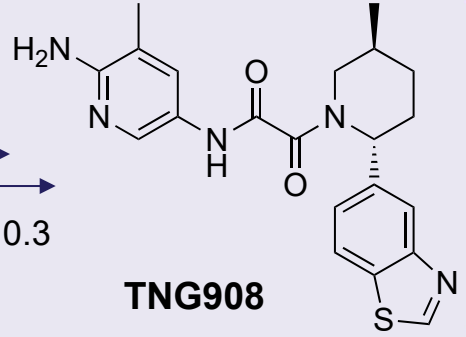
Evolution of biochemical HTS hit to clinical candidate TNG908

$K_{i,\ app,\ MTA}$ (μM)	0.6 (5x selective)
SDMA IC_{50} (μM)	-
Viability GI_{50} (μM)	-
$LogD_{7.4}$, MW	2.8, 326
$LipE_{LogD}$	4.2 (K_i)



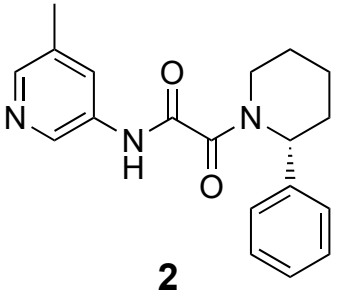
1

Tanimoto = 0.3



TNG908

$K_{i,\ app,\ MTA}$ (μM)	0.0002
SDMA IC_{50} (μM)	0.009
Viability GI_{50} (μM)	0.1 (15x)
$LogD_{7.4}$, MW	2.4, 410
$LipE_{LogD}$	9.2 (K_i), 5.7 (PD)



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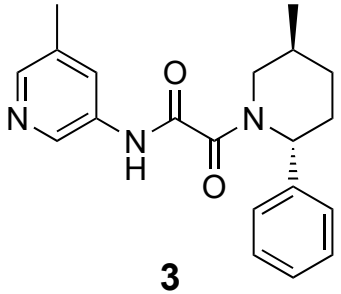

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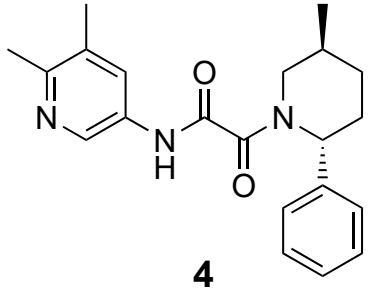

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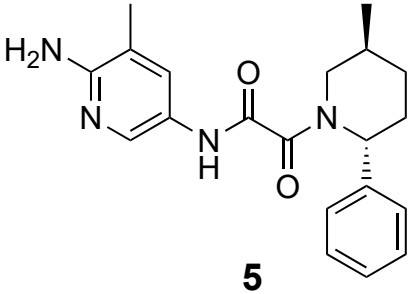
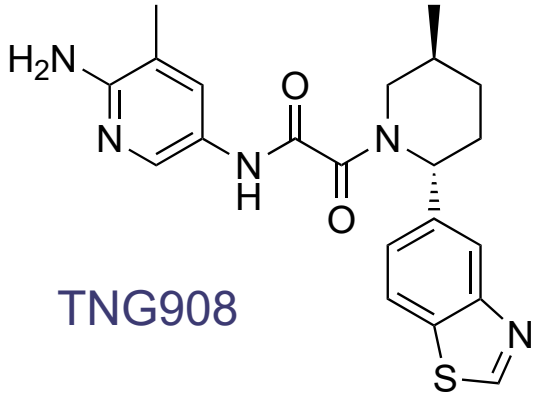


5

$K_{i,\ app,\ MTA}$ (μM)	0.2 (6x selective)	0.009	< 0.003	< 0.003
SDMA IC_{50} (μM)	-	3.5 (> 3x)	0.12	0.017
Viability GI_{50} (μM)	-	-	3.5 (> 5x)	0.4 (14x)

TNG908 is currently being studied in a Ph1/2 clinical trial NCT05275478

Goals for differentiation from TNG908



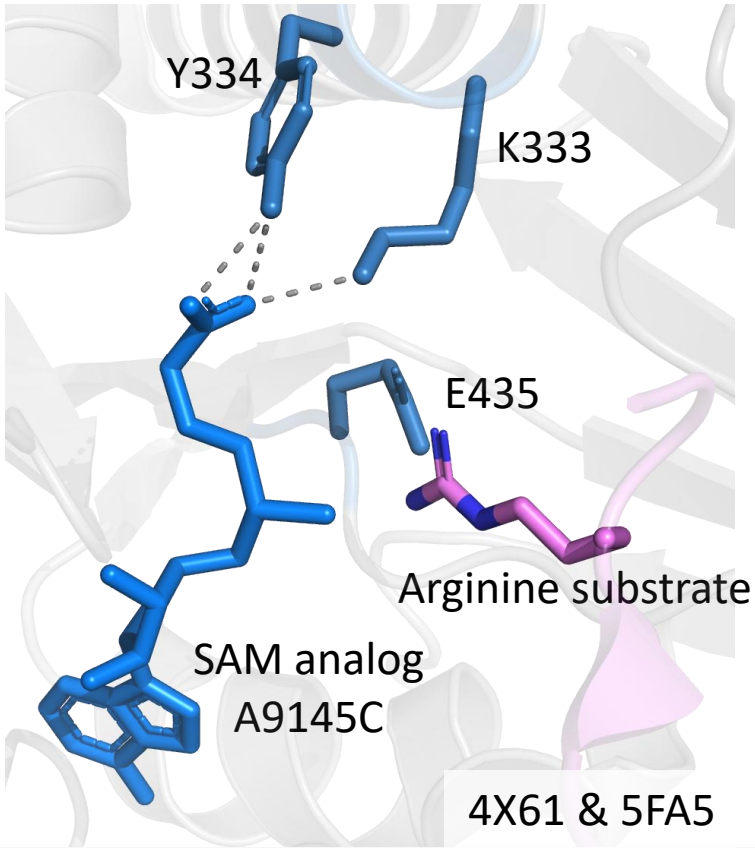
TNG908

	TNG908	2nd Generation Targets
Potency	Viability GI_{50} = 0.1 µM	> 1 log improvement
Selectivity	~ 15x vs WT (HAP1)	> 30x vs WT
PK	Projected BID human dose	QD, increase $T_{1/2}$
DDI risk	Moderate risk (CYP3A4)	Low *in vitro* signal at therapeutic concentration

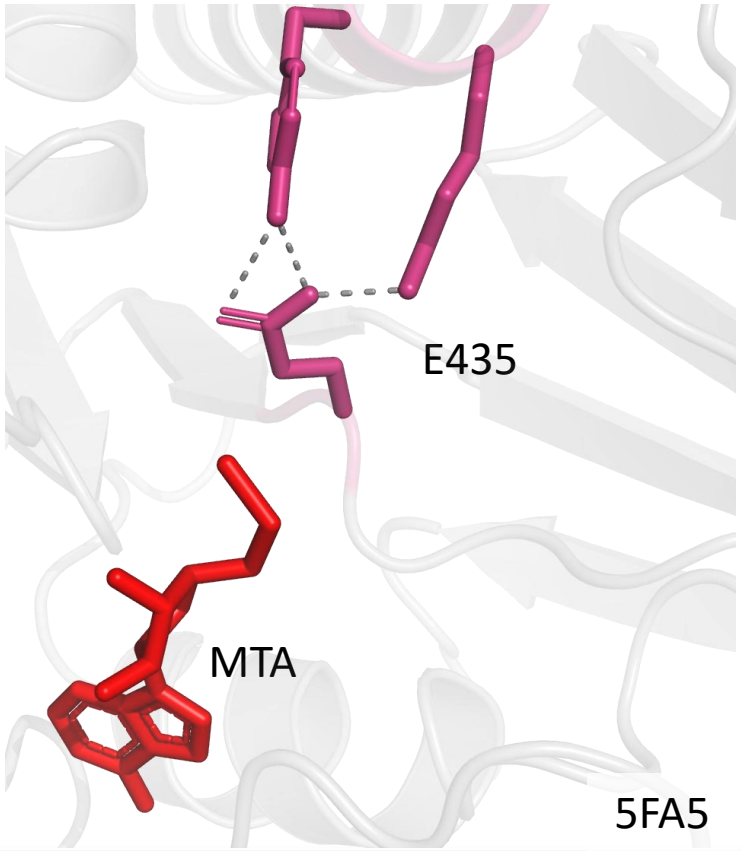
BID: twice a day; QD: once a day; PK: pharmacokinetics; DDI: drug-drug interaction; CYP3A4: cytochrome P450 3A4

Glutamate 435 rotamer-lock is key to selective binding with MTA

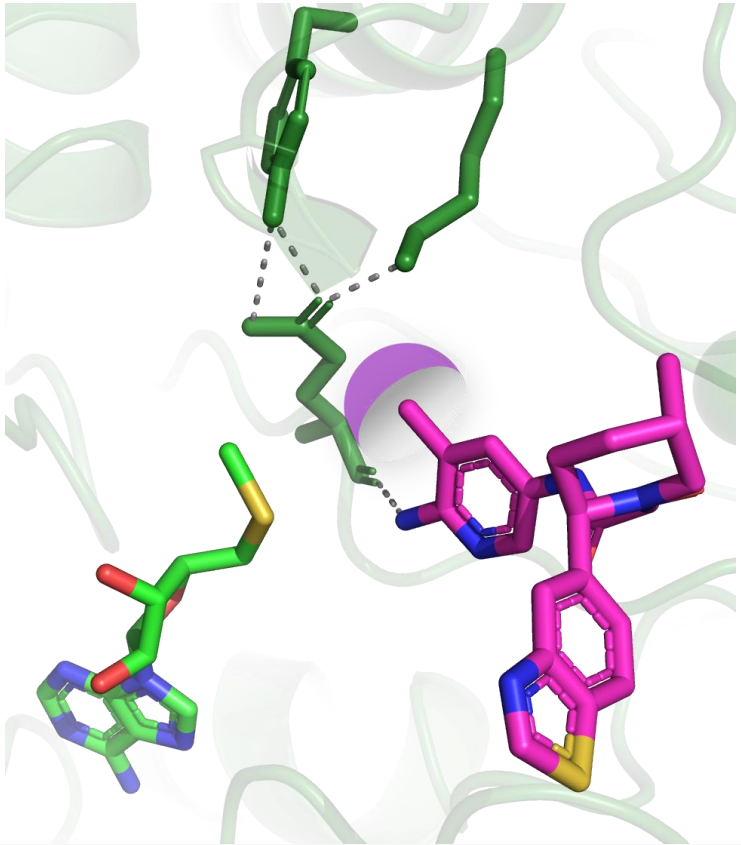
- SAM engages Y334/K333 in bioactive state
- E435 folded behind substrate



- E435 engages Y334/K333 sidechain when MTA is bound



- TNG908 engages E435 backbone C=O and sterically locks rotamer



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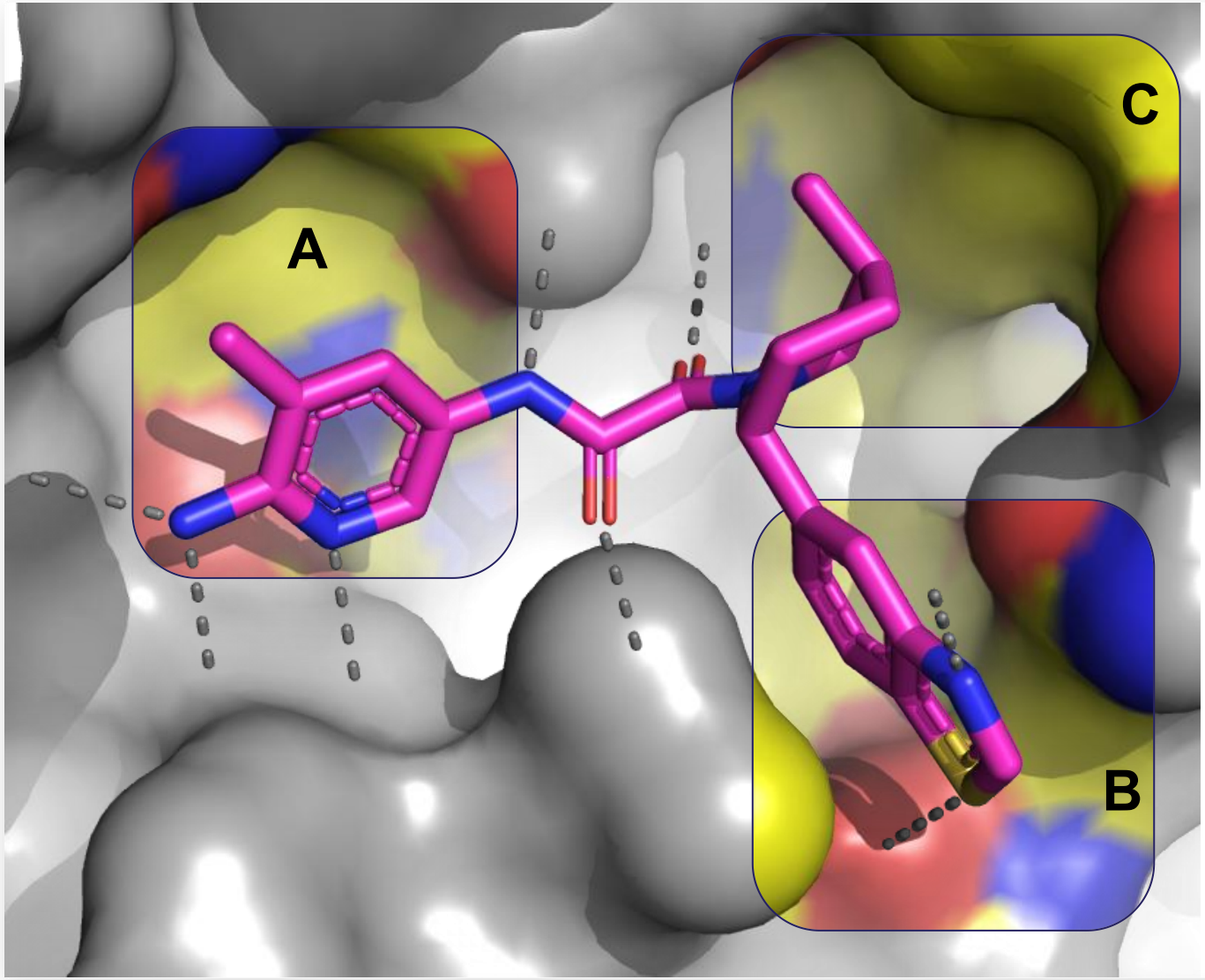
See Mavrakis, K. et al., Science 2016; Smith, C. et al, J Med Chem 2022 for other discussions of the movement of E435 in these systems

TNG908 binding analysis suggests areas for further exploration



- Aminopyridine near MTA/SAM binding pocket, H-bonds to E435, E444, π-stacks with F327
- Oxamide NH and C=Os engaged in H-bonds
- Other favorable VdW interactions and polar interactions

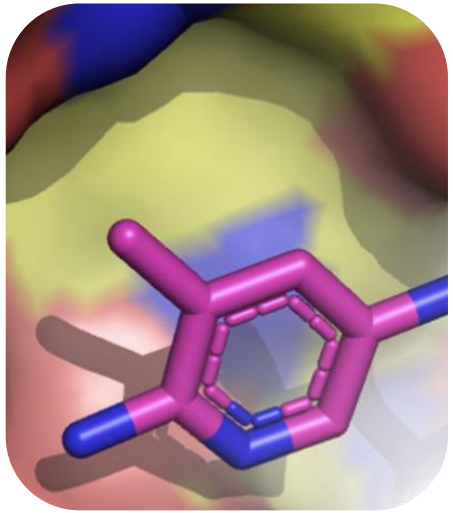
Hypotheses to improve potency and selectivity:

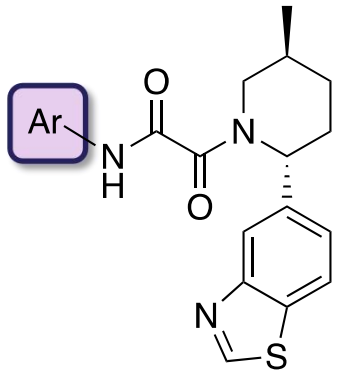
A. MTA/SAM pocket
   - Reinforce E435 rotamer lock

B. Benzothiazole region
   - Additional polar interactions

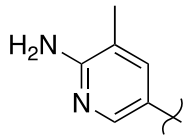
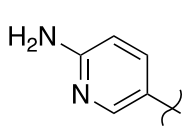
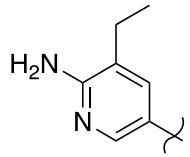
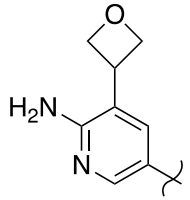
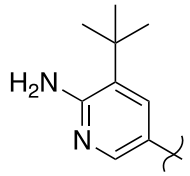
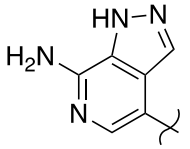
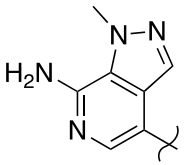
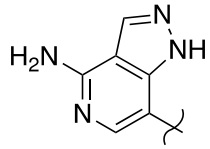
C. Small pocket near piperidine

Moderate SAR tolerance with high impact on potency and selectivity



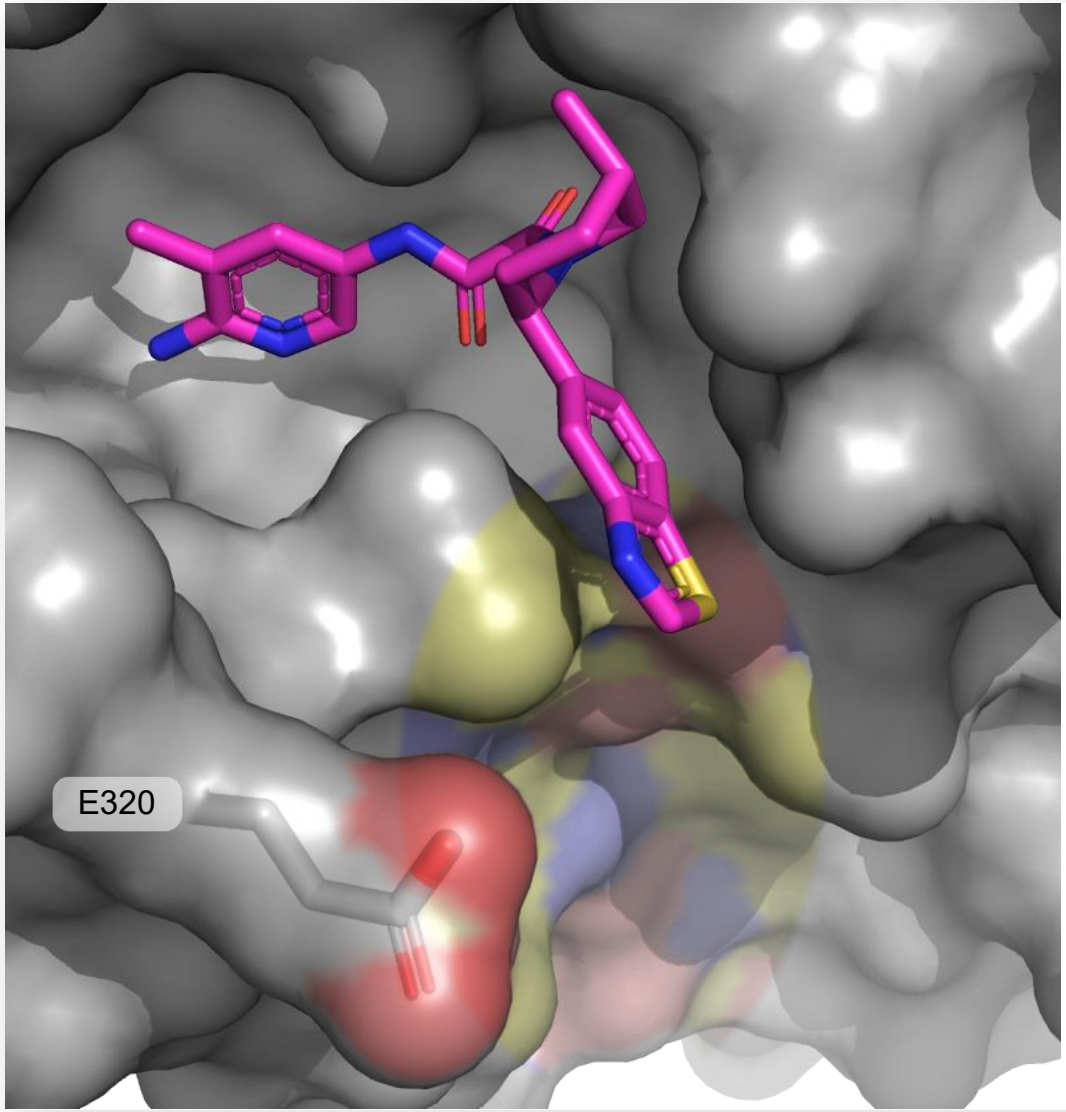


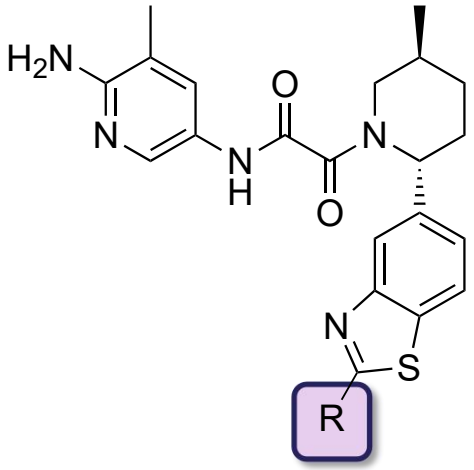
- Bicyclic systems can increase potency > 1 log
- Lipophilicity is not driving potency
- Limited size tolerance but large impact on selectivity

								
SDMA IC_{50} (μM)	0.009	0.073	0.009	0.006	0.11	0.004	0.002	0.0009
Viability GI_{50} (μM), selectivity over MTAP WT	0.1 15x	0.97 1.4x	0.082 43x	0.059 50x	2.8 7x	0.04 3x	0.01 40x	0.005 30x
$hCl_{int,\ mic}$ (μL/min/mg)	14	–	30	15	97	33	24	23
	TNG908							

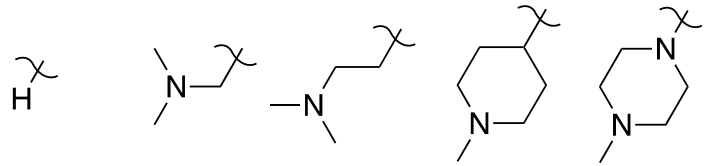
$hCl_{int,\ mic}$: intrinsic clearance in human liver microsomes; SDMA: symmetric dimethylarginine

Benzothiazole C2 substitution has broad impact on profile



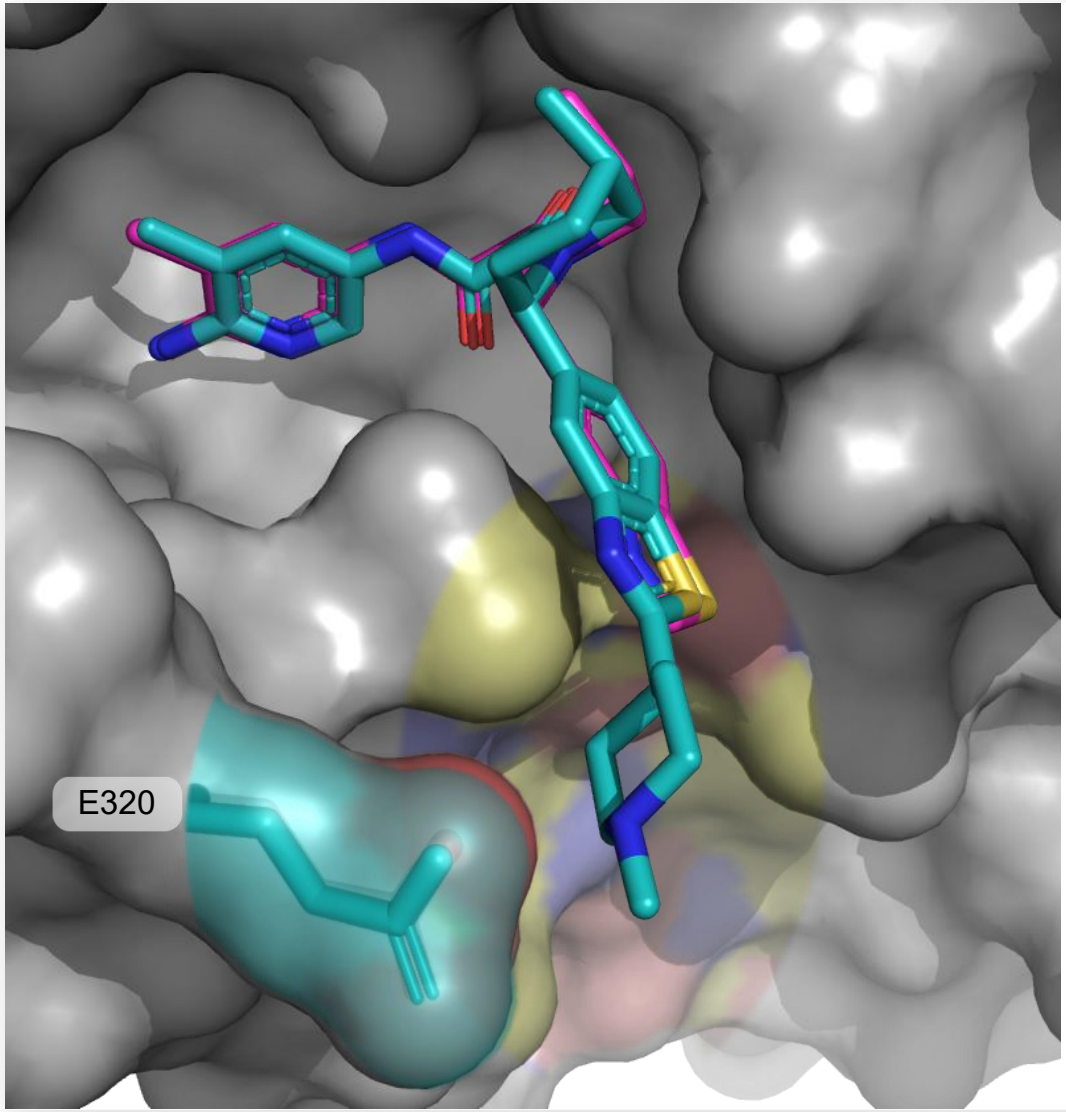


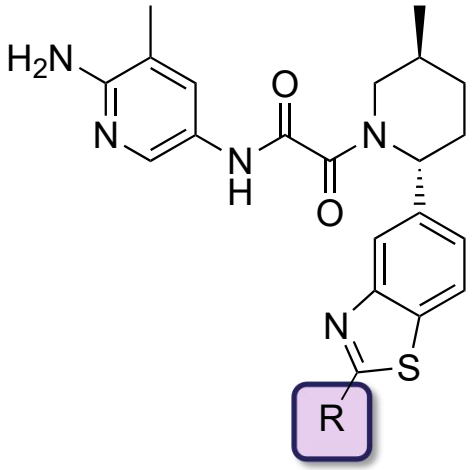
- Salt bridge with E320 gains up to 14-fold potency
- Selectivity largely unchanged
- Metabolic stability variable



SDMA IC_{50} (μM)	0.009	0.01	0.01	0.001	0.004
Viability GI_{50} (μM)	0.10	0.03	0.02	0.007	0.027
Selectivity over MTAP WT GI_{50}	15	11	7	8	10
$hCl_{int,\ mic}$ (μL/min/mg)	14	30	10	10	57
	TNG908				

Benzothiazole C2 substitution has broad impact on profile





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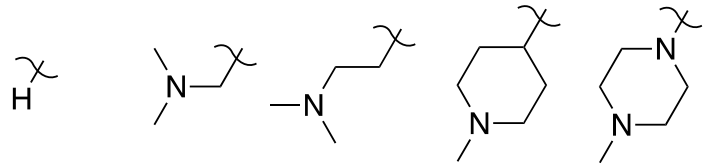

	TNG908				
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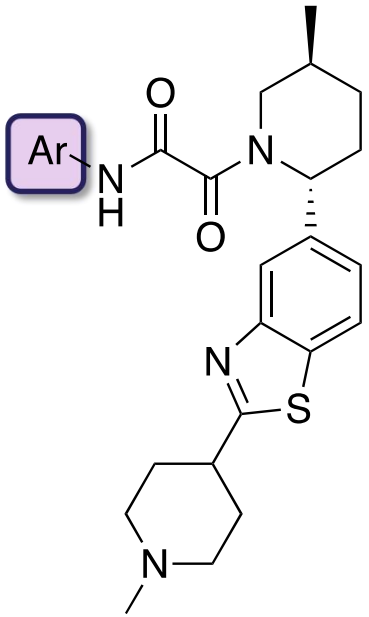
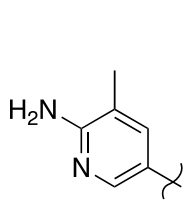
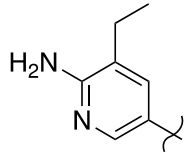
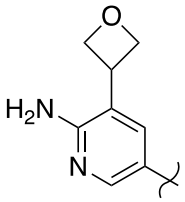
Non-additive SAR between ends of the molecules and unexpected selectivity modulation at benzothiazole C2

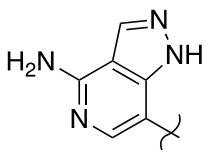


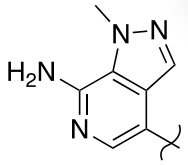
- Bicycles are potent but show reduced selectivity
- Piperidine rescues metabolic stability in previously unstable cases

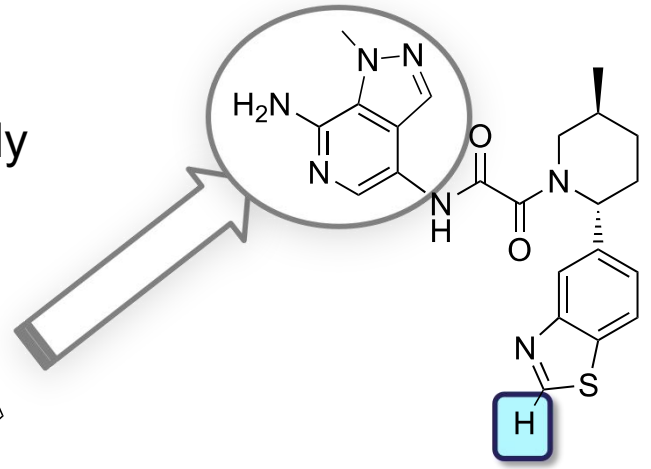






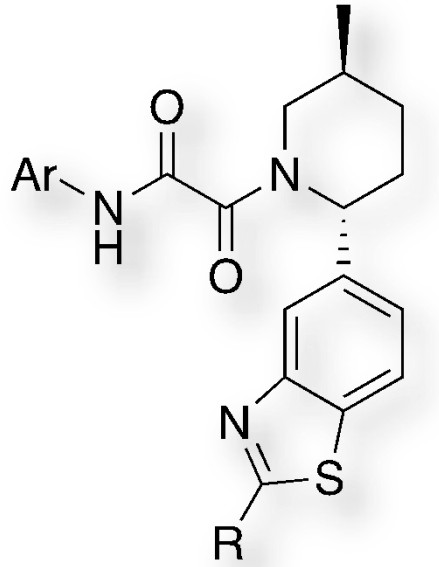


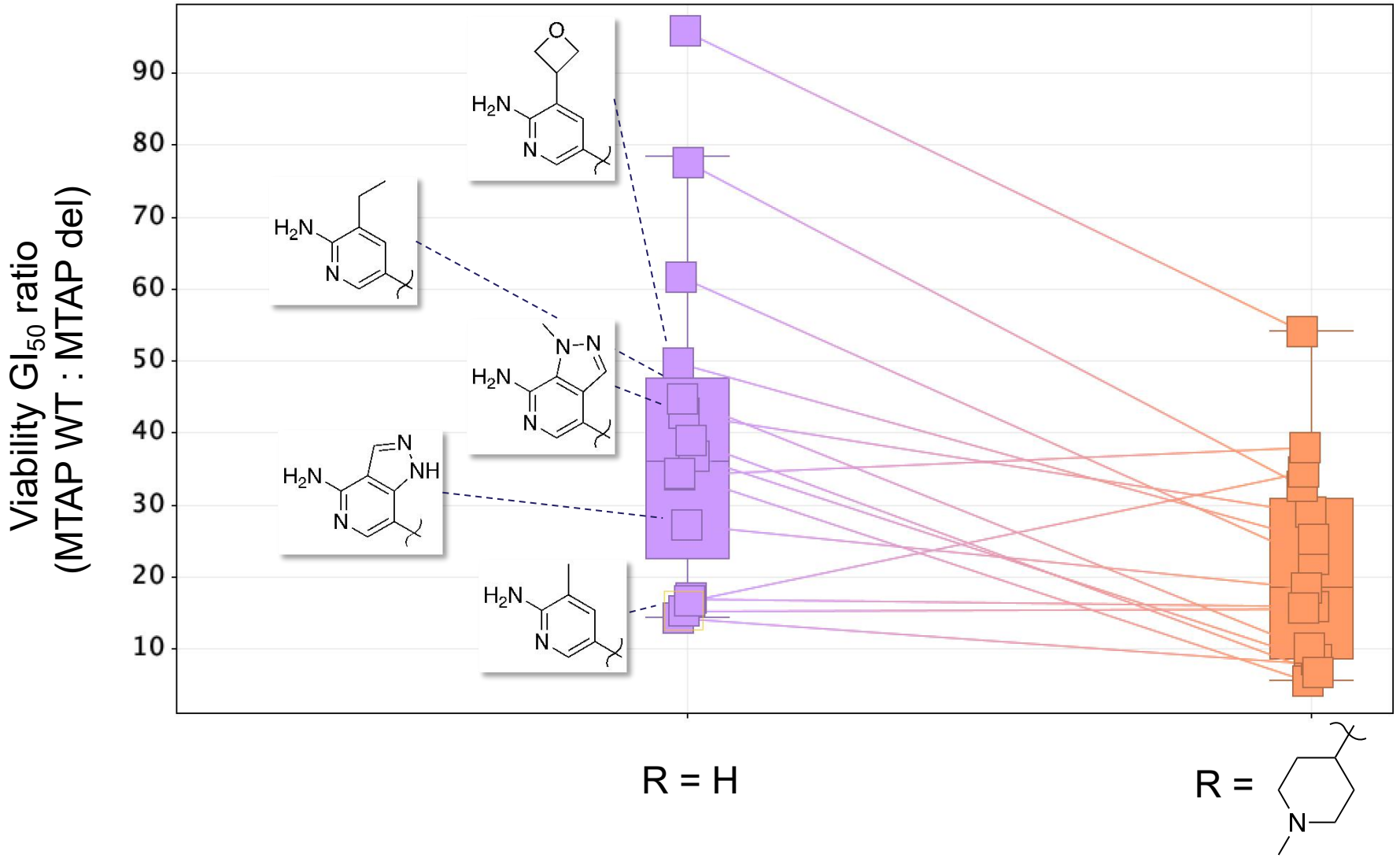




SDMA IC_{50} (μM)	0.001	0.0008	0.002	0.001	0.001	0.002
Viability GI_{50} (μM)	0.007	0.003	0.007	0.002	0.004	0.01
Selectivity (to $GI_{50, WT}$)	8	30	24	6	8	40
$hCl_{int, mic}$ (μL/min/mg)	10	15	< 10	18	15	24

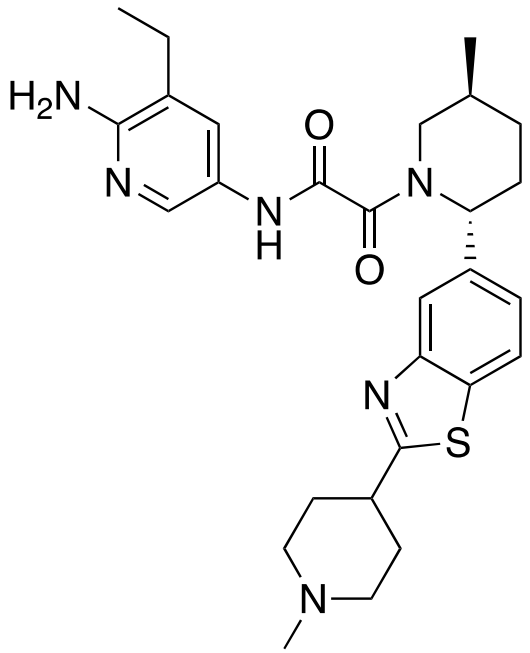
MMPs indicate general erosion of selectivity with C2 Me-piperidine





MMPs: matched molecular pairs (for introduction see Dossetter, A. G.; Griffen, E. J.; Leach, A. G. “Matched Molecular Pair Analysis in Drug Discovery” Drug Disc Today 2013, 18, 724)

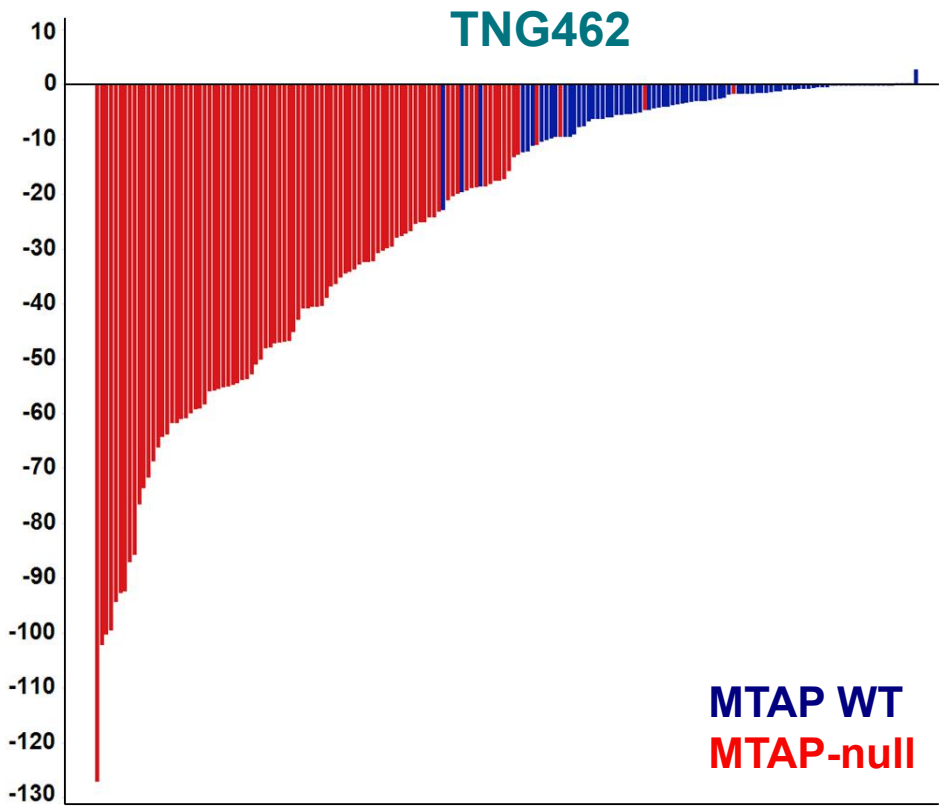
TNG462 preclinical profile

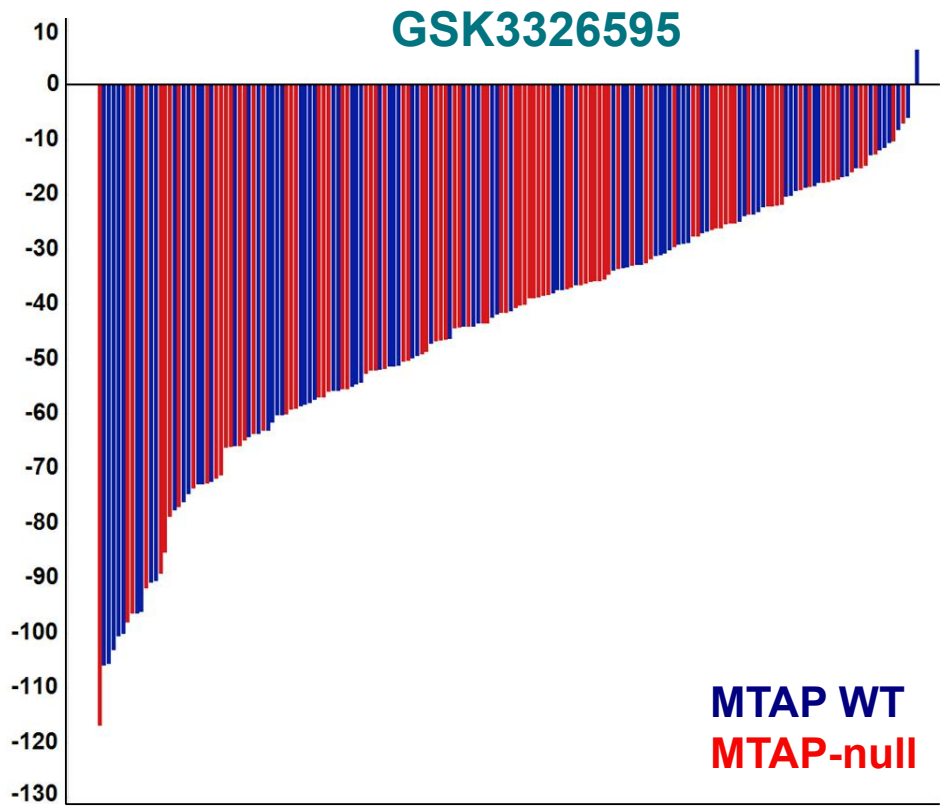


TNG462	
MW, $LogD_{7.4}$, TPSA	520, 2.2, 104
Solubility in SGF, SIF (mM)	> 24, > 6
Cellular PD IC_{50}, viability GI_{50}	800 pM, 3 nM
WT viability selectivity	45x (average of 4 isogenic pairs)
$T_{1/2}$ d, c (hrs)	14, 20
%F d, c	52, 33
$Cl_{int,\ hep}$ h, d, c (µL/min/10^6)	3, 9, 12
DDI risk	Low risk of CYP or transporter mediated DDI at therapeutic doses
hERG IC_{50}, µM	10
Methyl Transferase Panel	No concerns
Eurofins Safety Panel	No concerns

SGF: simulated gastric fluid; SIF: simulated intestinal fluid; $hCl_{int,\ mic}$: intrinsic clearance in human liver microsomes; $hCl_{int,\ hep}$: intrinsic clearance in human hepatocytes; DDI: drug-drug interaction

TNG462 antiproliferative activity is selective for MTAP-null models across histologies



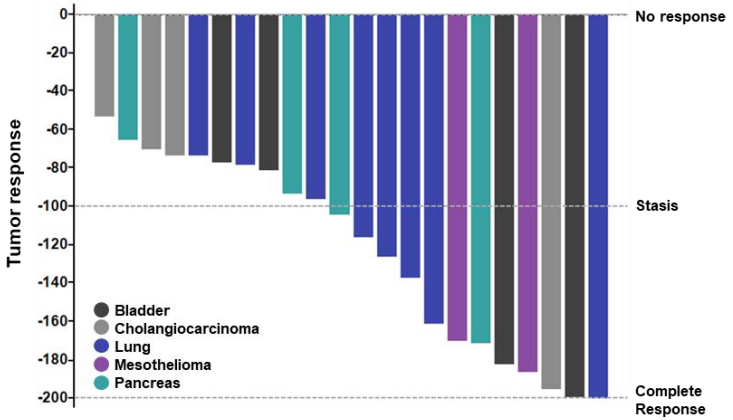


- 180 cancer cell lines representing multiple cancer lineages including NSCLC, PDAC, bladder, CNS, and heme malignancies
- 7-day CellTiter-Glo assay
- Maximum effect at concentration equal to 10X HAP1 MTAP-null GI_{50}
- TNG462 is >25x more potent than GSK3326595 in MTAP-null cell lines *in vitro*

TNG462 drives durable tumor regressions across histologies

Efficacy is not histology-biased

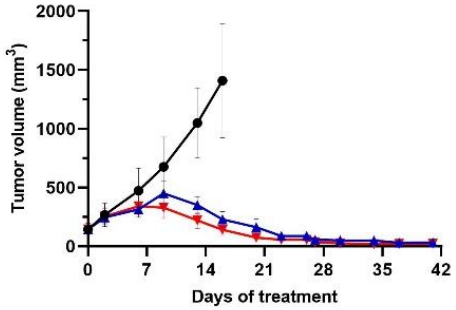
Multiple histologies
MTAP-null PDX



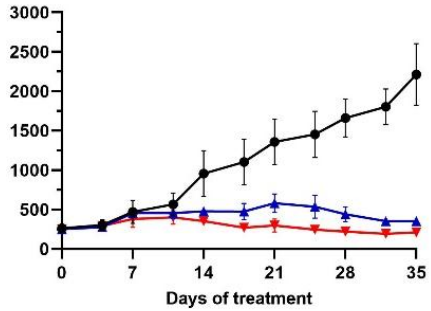
Tumor regression achieved in ~55% of models

Deep, durable regressions in MTAP-del PDX models

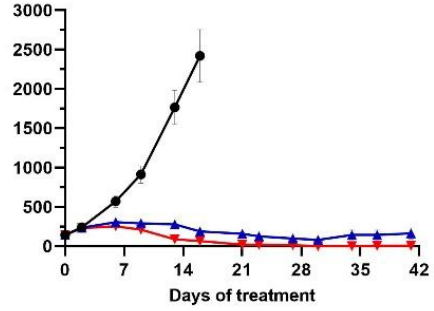
Mesothelioma
Continuous Tx



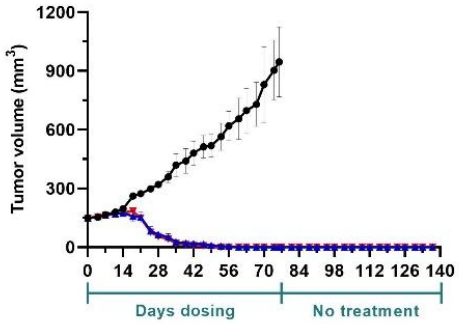
NSCLC (adenocarcinoma)
Continuous Tx



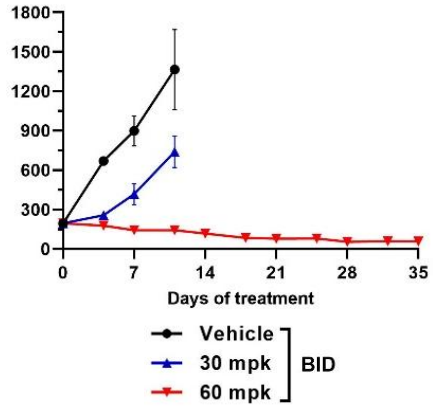
Cholangiocarcinoma
Continuous Tx



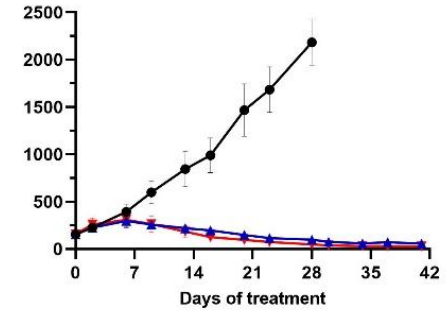
NSCLC (squamous)
Sustained response



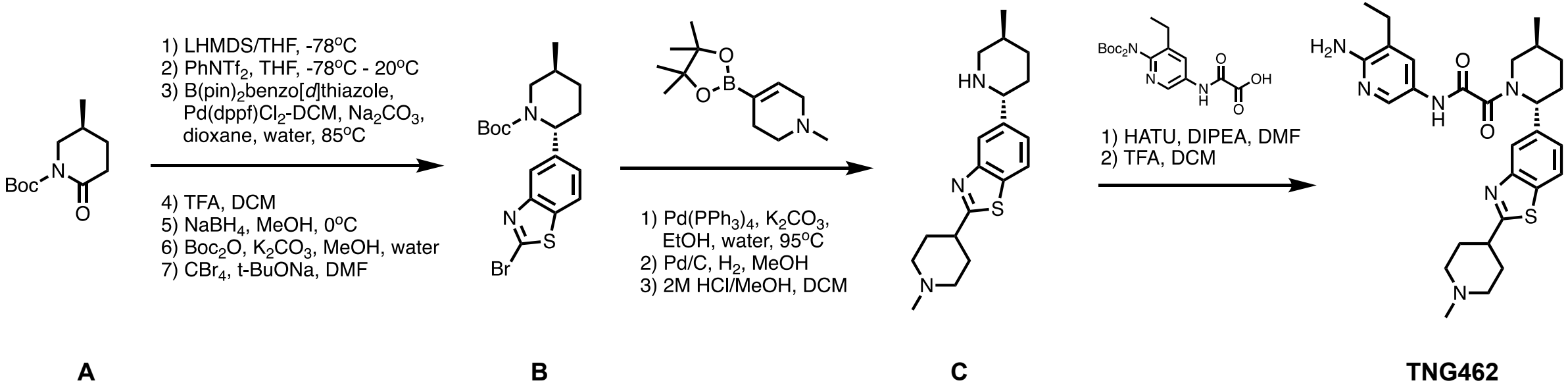
Pancreatic
Continuous Tx



Bladder
Continuous Tx



Synthesis of TNG462



Many thanks to Enamine (Oleg Michurin, Team Lead) and WuXi (Wei Chen, Chemistry Lead)

TNG462: A novel, selective, MTA-cooperative inhibitor of PRMT5

- Highly potent, selective MTA-cooperative inhibitor of PRMT5
- Long predicted human $T_{1/2}$, predicted to be suitable for QD dosing
- Robust single agent efficacy across histologies in PDX models
- Preclinical *in vivo* toxicology observations align with MTAP-WT selectivity
- Low risk of CYP3A4 and transporter mediated DDIs at therapeutic doses
- Currently in a Phase 1/2 clinical trial

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WuXi Chemistry team


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