Oxamide-based MTA-cooperative PRMT5 inhibitor discovery including Vopimetostat and TNG456

John P. Maxwell

September 18, 2026

TANGO therapeutics™

Disclosures

John P. Maxwell is an employee and shareholder of Tango Therapeutics, Inc.

Leaders in PRMT5 science, advancing to late-stage development based on compelling clinical data

Well-funded to execute clinical development plan

Compelling data for vopimetostat + RAS(ON) inhibitors supports development in **1L PDAC**



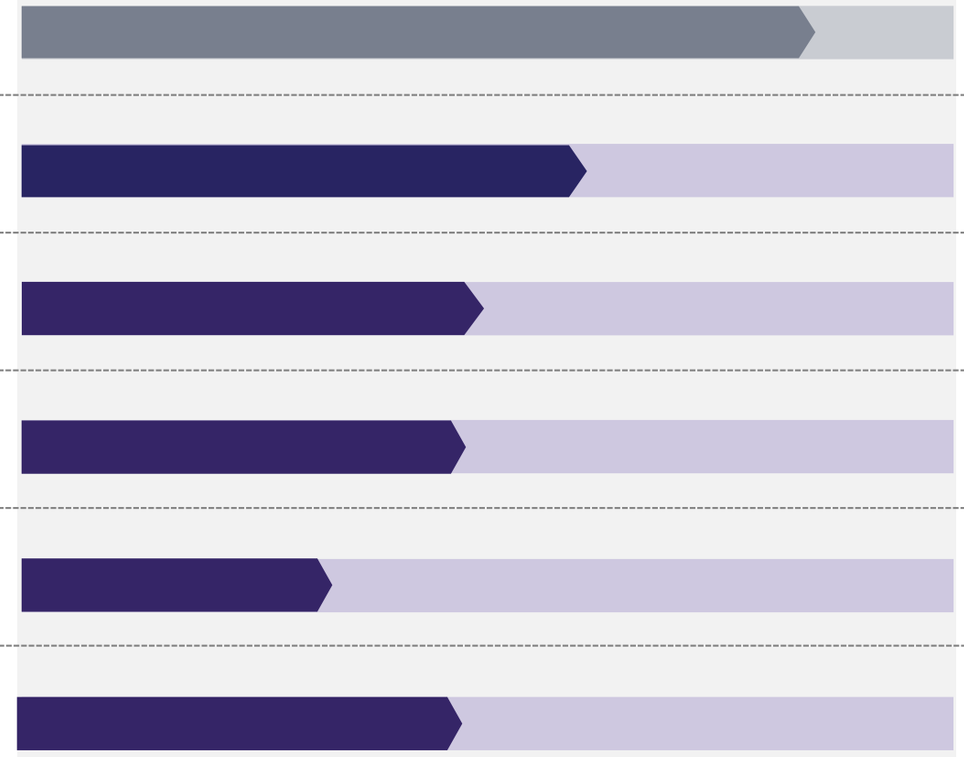
Vopimetostat is a highly potent and selective PRMT5 inhibitor with **first- and best-in-class potential**

PRMT5 franchise potential with **vopimetostat** and CNS-penetrant **TNG456** in lung, GBM and additional tumor types

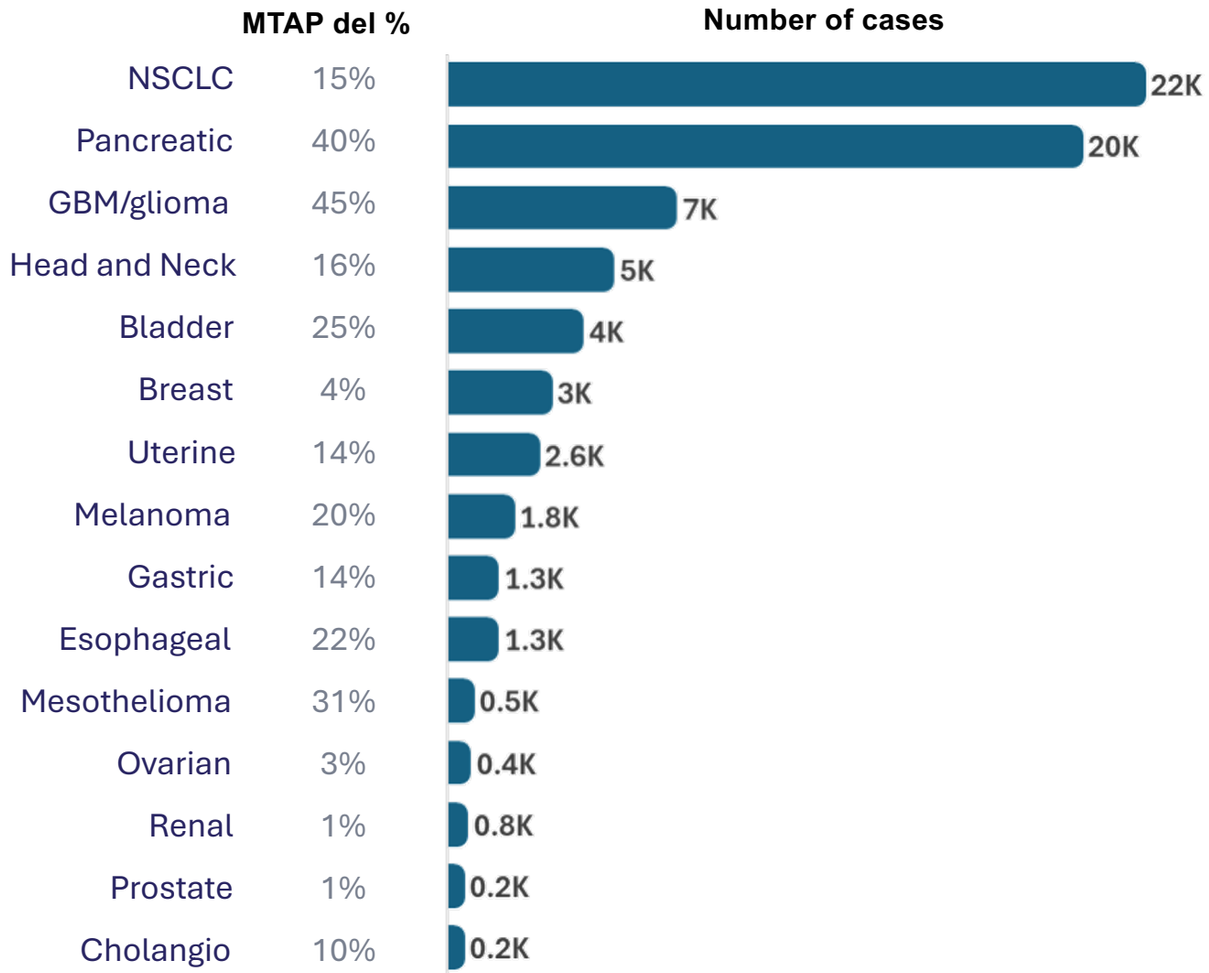
Wholly owned pipeline targeting cancers with MTAP loss

MOLECULE	INDICATION	COMBINATION	CLINICAL PHASE	STATUS
			PRE-CLINICAL / PHASE 1/2 / PHASE 3	
Vopimetostat	1L PDAC[a]	+ daraxonrasib		Study design to be finalized 2H 2026
	2L PDAC	+ daraxonrasib		Expansion of ongoing Phase 1/2 study
	PDAC, Lung	+ daraxonrasib + zoldonrasib		Additional data 2H 2026
	Solid tumors with MTAP loss	Monotherapy		Lung data 2H 2026
	PDAC, Lung	+ ERAS-0015		Study start 2H 2026
TNG456	Glioblastoma	Monotherapy		Phase 1/2 data in 2026

[a]Planned



~60,000 patients with MTAP del metastatic cancers annually in the US



Multiple indication expansion opportunities (NSCLC, GBM)

Patient population sizes estimated using data from SEER, Kantar, TCGA PanCancer Atlas and other sources. PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer.

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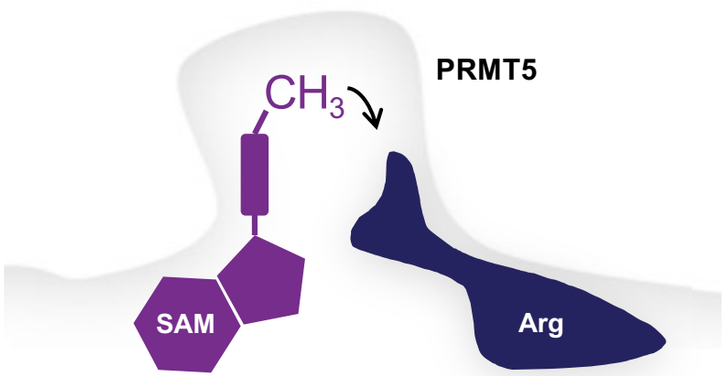
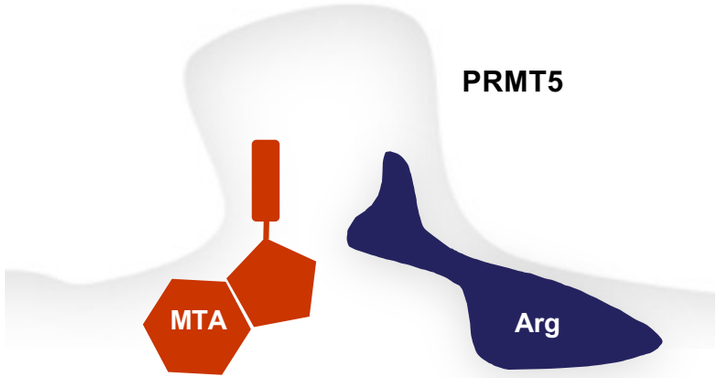
MTA-cooperative PRMT5 inhibitors are designed to work with MTA

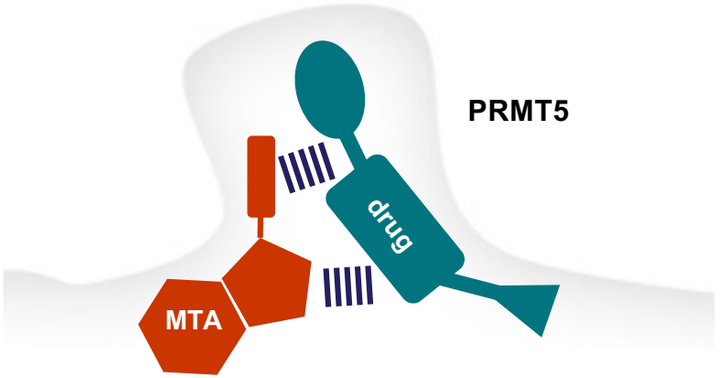
Cells with MTAP

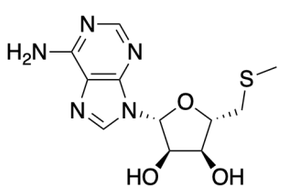


MTAP-deleted cancer cells



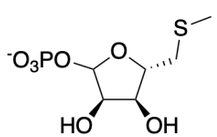
MTAP deleted cancer cells + MTA-cooperative inhibitor





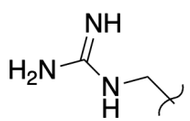
MTA (methylthioadenosine)

MTAP

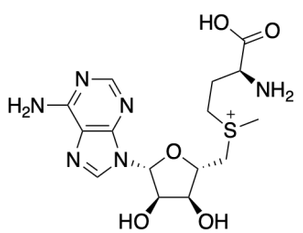


MTR-1P

Arginine sidechain

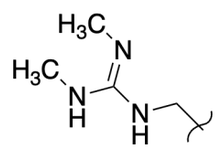


PRMT5



SAM ((*S*)-adenosylmethionine)

SDMA (symmetric dimethyl Arg)



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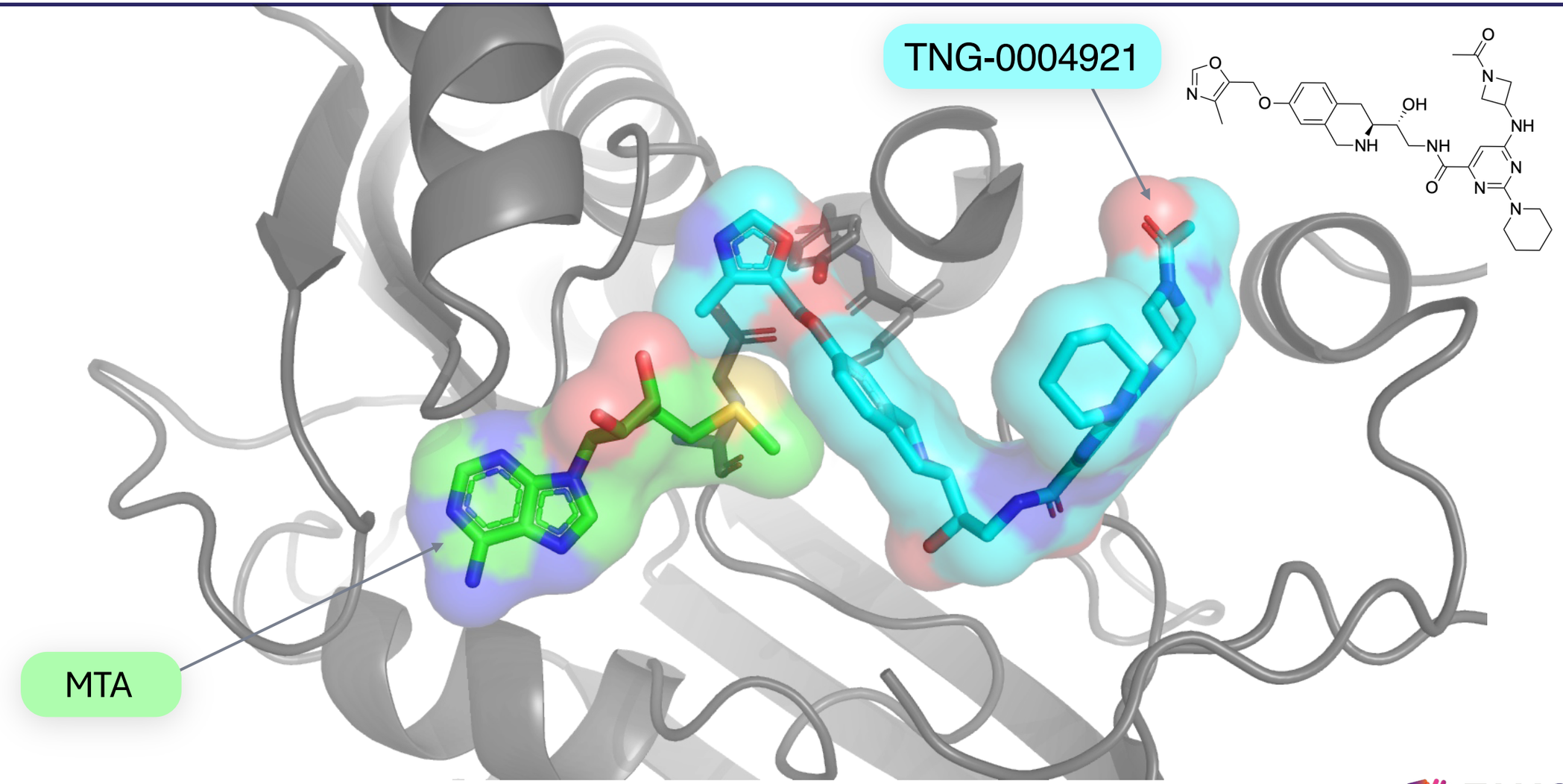
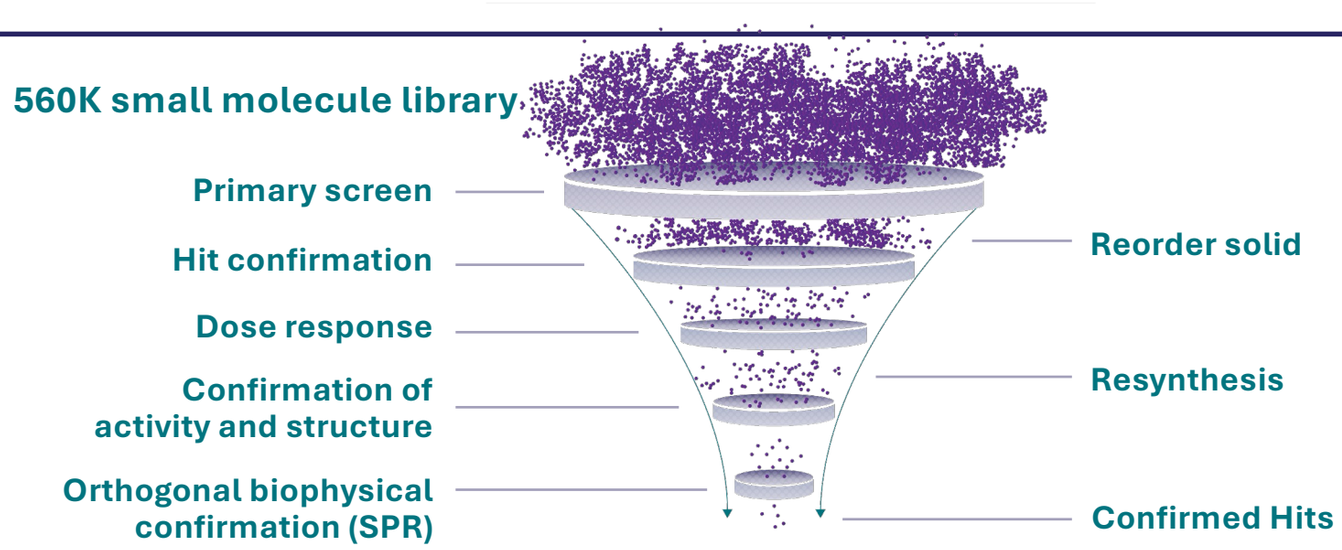
Tango was first to disclose MTA-cooperative PRMT5 inhibitors

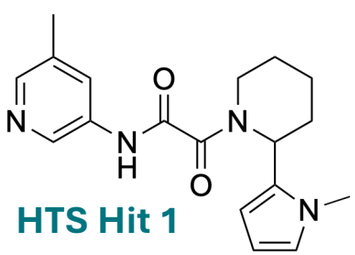


a) Cottrell, K. M.; Maxwell, J. P.; Whittington, D. A. *Compounds and Methods of Use*, US 11,077,101, **2021** b) Cottrell, K. M.; Whittington, D. A.; Briggs, K. J., et al., "MTA-Cooperative PRMT5 Inhibitors: Mechanism Switching Through Structure-Based Design", J Med Chem **2025**, 68, 4217-4263

TANGO therapeutics

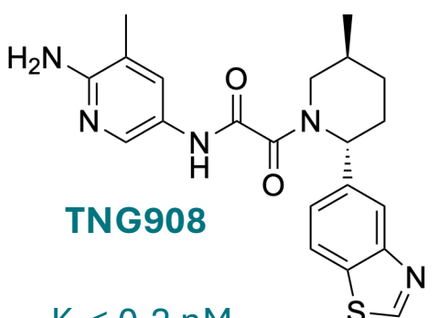
From high-throughput screening hit to three clinical molecules





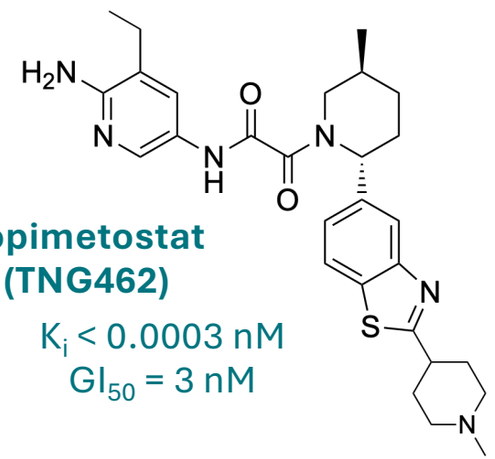
HTS Hit 1

K_i = 600 nM
GI_{50} > 100 µM



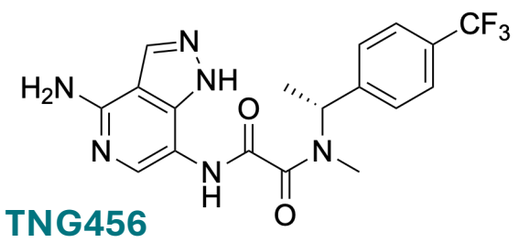
TNG908

K_i < 0.2 nM
GI_{50} = 120 nM



Vopimetostat (TNG462)

K_i < 0.0003 nM
GI_{50} = 3 nM



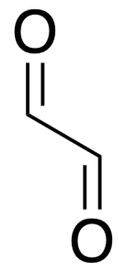
TNG456

K_i < 0.002 nM
GI_{50} = 20 nM

Cottrell, K. M.; Briggs, K. J. et al., J Med Chem: **2024**, 67, 6064-6080 (TNG908); **2025**, 68, 5097-5119 (TNG462); **2026**, 69, 12853-12869 (TNG456)

TANGO therapeutics

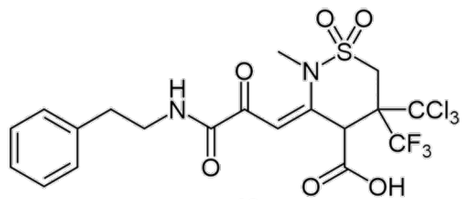
1,2-Dicarbonyl is widely considered a structural alert or reactive



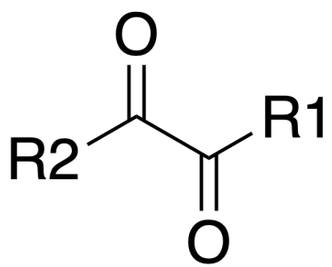
2011: “1,2-dicarbonyl: metabolically unstable/potential toxicity due to mutagenicity”

2016: “Trifluoromethyl ketone, aldehyde, and alpha_dicarbonyl FG filters show higher levels of promiscuity but are at the lower end of the high ranking”

2023: “…**48** contains a potentially mutagenic 1,2-dicarbonyl group”

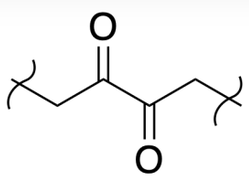
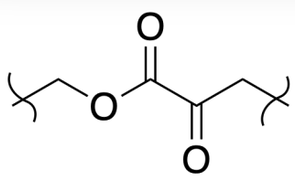
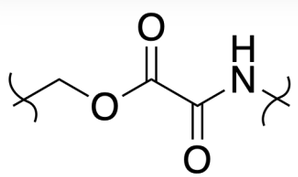


48



R1 = C; R2 = C, O

R1 = N; R2 = O

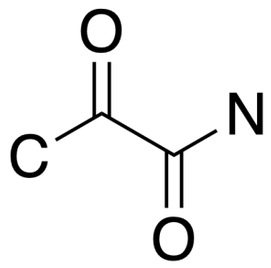
α,β-diketone	α-ketoester	oxamate
		

- reactive
- subject to hydrolysis
- frequent synthetic building blocks
- generally, not found in medchem literature

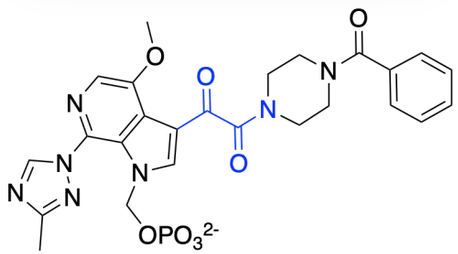
(a) Pearce, B. C.; Sofia, M. J.; Good, A. C.; Drexler, D. M.; Stock, D. A. An Empirical Process for the Design of High-Throughput Screening Deck Filters. *J. Chem. Inf. Model.*, **2016**, 46, 1060-1068. (b) Huggins, D. J.; Venkitaraman, A. R.; and Spring, D. R. Rational Methods for the Selection of Diverse Screening Compounds. *ACS Chem. Biol.*, **2011**, 6, 3, 208-217. (c) Rishton, G. M.; Reactive Compounds and in vitro False Positives in HTS. *Drug Discovery Today.* **1997**, 2, 9, 382. (d) Ivanenkov, Y,.; Zagribelnyy, B.; Malyshev, A.; Evteev, S.; Terentiev, V.; Kamya, P.; Bezrukov, D.; Aliper, A.; Ren, F.; Zhavoronkov, A. The Hitchhiker’s Guide to Deep Learning Driven Generative Chemistry. *ACS MedChem Lett.*, **2023**, 14, 901-915.

TANGO therapeutics

Other dicarbonyls are less common, but have strong precedent

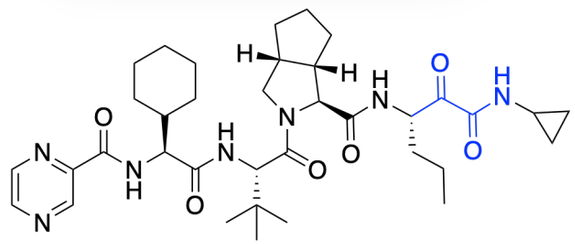


glyoxamide

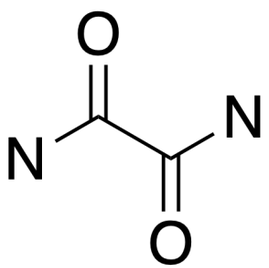


Fostemsavir (HIV-1 attachment inhibitor)

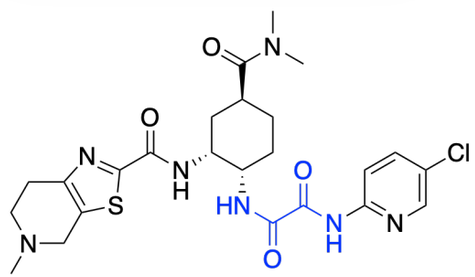
α-ketoamide



Telaprevir (HCV protease inhibitor)



oxamide



Edoxaban (Factor Xa inhibitor)

- Chemically unreactive in biorelevant setting
- Not electrophilic
- Stable in biological media
- Viable substructure for medicinal chemistry optimization

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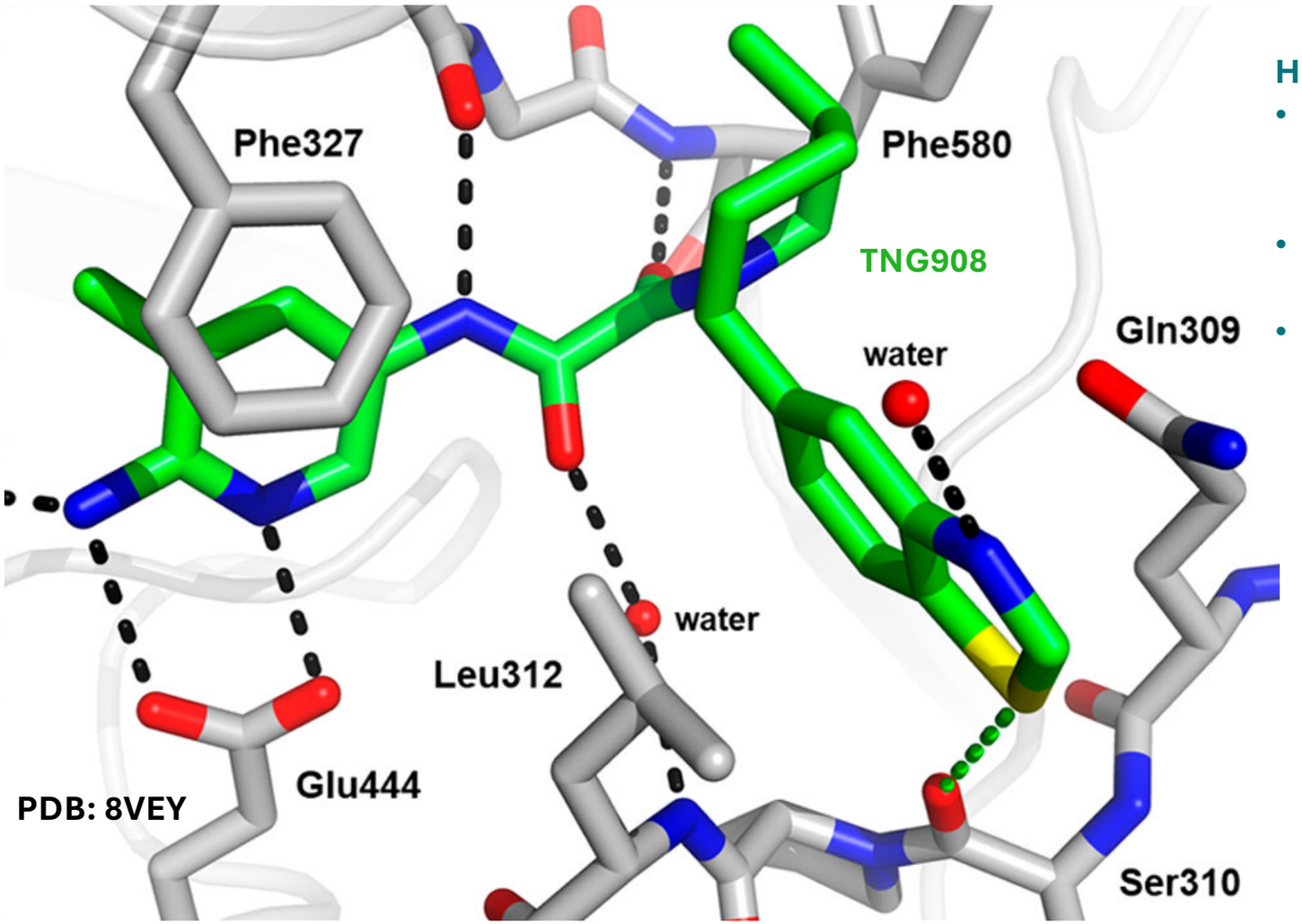
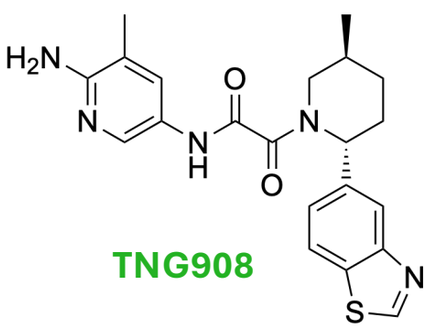
Oxamide scaffold enabled dense packing of ligand-protein interactions



Highly optimized ligand-protein contacts

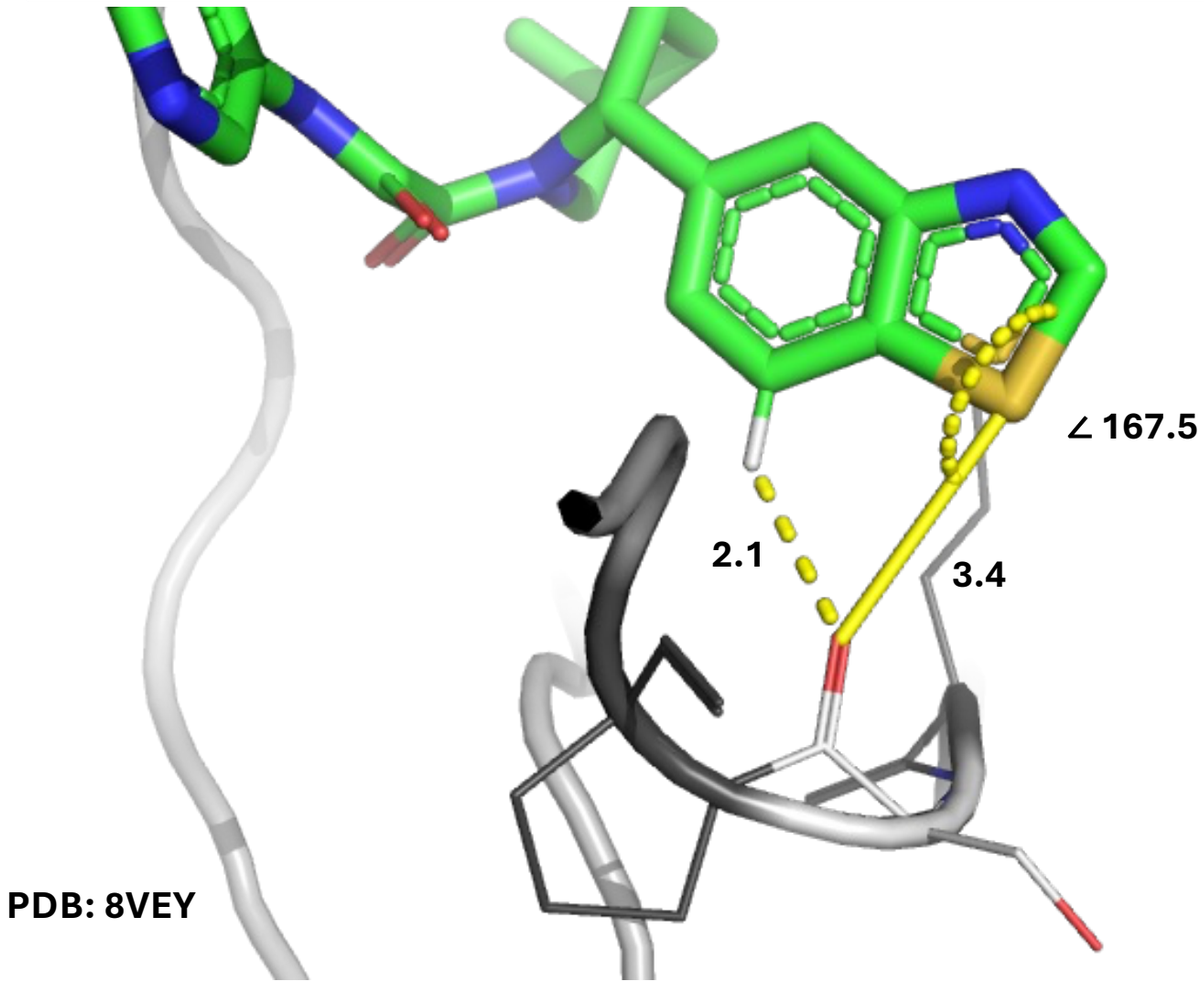
- Aminopyridine near MTA/SAM binding pocket, H-bonds to E435, E444, π-stacks with F327
- Oxamide NH and C=Os engaged in H-bonds
- Other favorable VdW interactions and polar interactions



TNG908

Cottrell, K. M.; Briggs, K. J. et al., J Med Chem: **2024**, 67, 6064-6080

Benzothiazole bidentate interaction with backbone key design feature



PDB: 8VEY

Highly optimized ligand-protein contacts

- 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

Key benzothiazole interactions

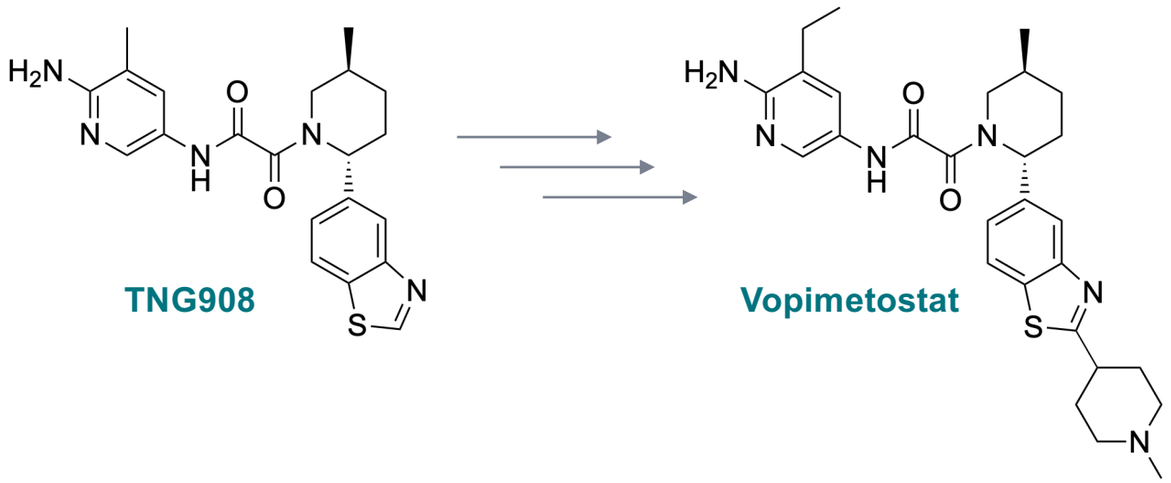
- Bidentate carbonyl contact with S and H-Ar
- S--O=C, 3.4 Å (C-S σ* orbital)
- H--O=C, 2.1 Å
- 167° dihedral angle (S-O-C)

- Important and underutilized interaction
- Gain ligand-protein contact without increased HBD

(a) Cottrell, K. M.; Briggs, K. J. et al., J Med Chem: **2024**, 67, 6064-6080. (b) Beno, B. R.; Yeung, K.-S.; Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A. A Survey of the Role of Noncovalent Sulfur Interactions in Drug Design. *J Med Chem* **2015**, *58* (11), 4383–4438. (c) Koebel, M. R.; Cooper, A.; Schmadeke, G.; Jeon, S.; Narayan, M.; Sirimulla, S. S···O and S···N Sulfur Bonding Interactions in Protein–Ligand Complexes: Empirical Considerations and Scoring Function. *J. Chem. Inf. Model.* **2016**, *56* (12), 2298–2309. (d) Zhang, X.; Gong, Z.; Li, J.; Lu, T. Intermolecular Sulfur···Oxygen Interactions: Theoretical and Statistical Investigations. *J. Chem. Inf. Model.* **2015**, *55* (10), 2138–2153.

TANGO therapeutics

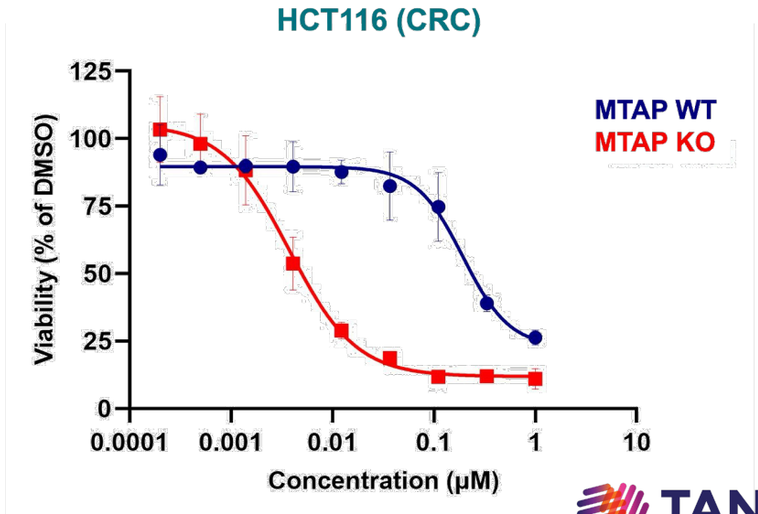
Vopimetostat potency, selectivity, and solubility improved vs TNG908



$K_{i,\ app,\ MTA}$ (nM)	0.2	< 0.0003
Viability GI_{50} (nM)	120	3
MTAP null selectivity	15x	45x
$LogD_{7.4}$, MW	2.4, 410	2.2, 520
$LipE_{LogD}$	9.2 (K_i)	10.3 (K_i)

Vopimetostat relative to TNG908

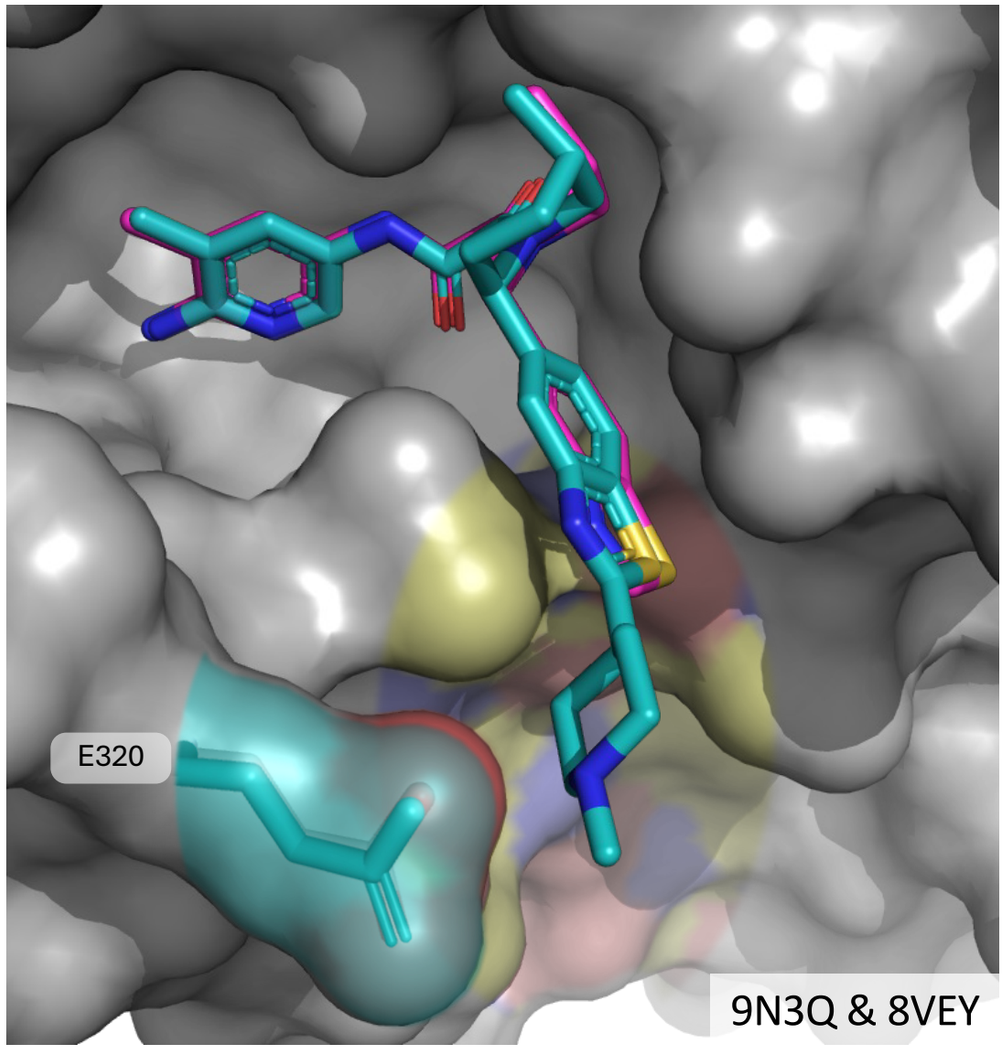
- > 700-fold increase in potency
- Increased selectivity for MTAP null cells
- Increased solubility (> 6 mM in SIF)
- Once-daily human dosing
- Currently in clinical trials

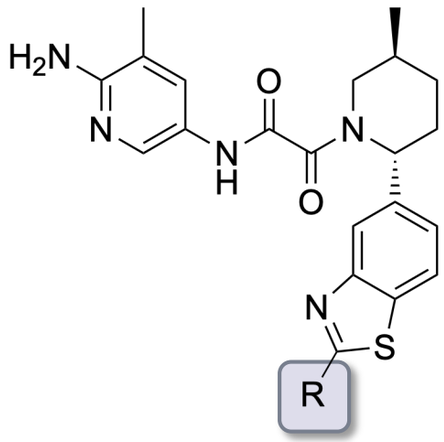


Cottrell KM, et al. J Med Chem **2025,** 68, 5097–5119

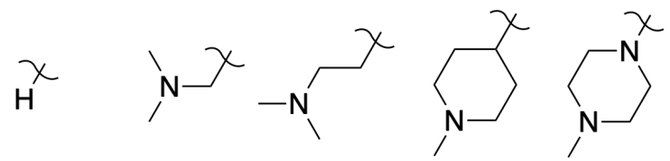
TANGO therapeutics

Increased potency via structure-based design of key interactions





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



	TNG908				
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

Cottrell KM, et al. J Med Chem **2025,** 68, 5097–5119

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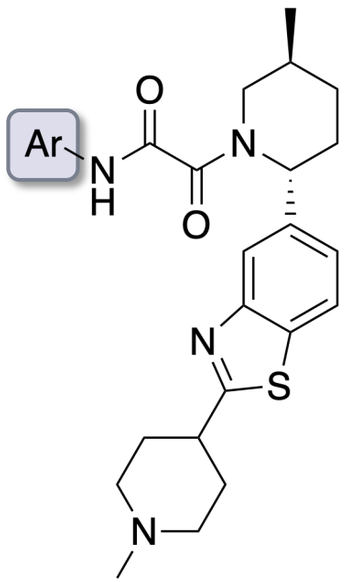
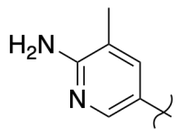
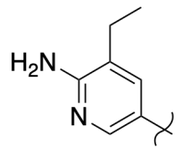
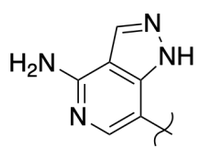
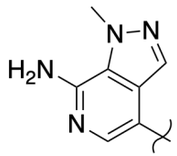
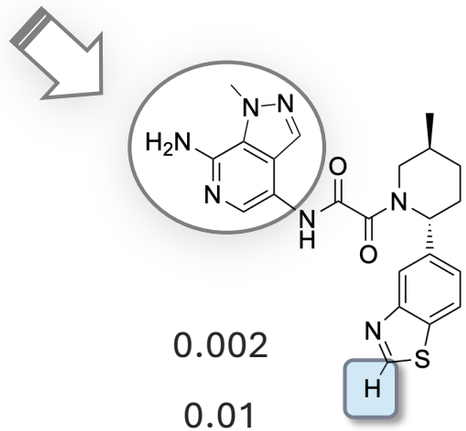
Selectivity dialed in through manipulation of both ends of molecule



				
SDMA IC_{50} (μM)	0.001	0.0008	0.001	0.001
Viability GI_{50} (μM)	0.007	0.003	0.002	0.004
Selectivity (to $GI_{50, WT}$)	8	45	6	8
$hCl_{int, mic}$ (μL/min/mg)	10	15	18	15
		Vopimetostat		



0.002
0.01
40
24

- Many left-hand side aromatic and non-aromatic groups explored
- Bicycles are potent but show reduced selectivity if E320 also engaged
- Piperidine rescues metabolic stability in previously unstable cases

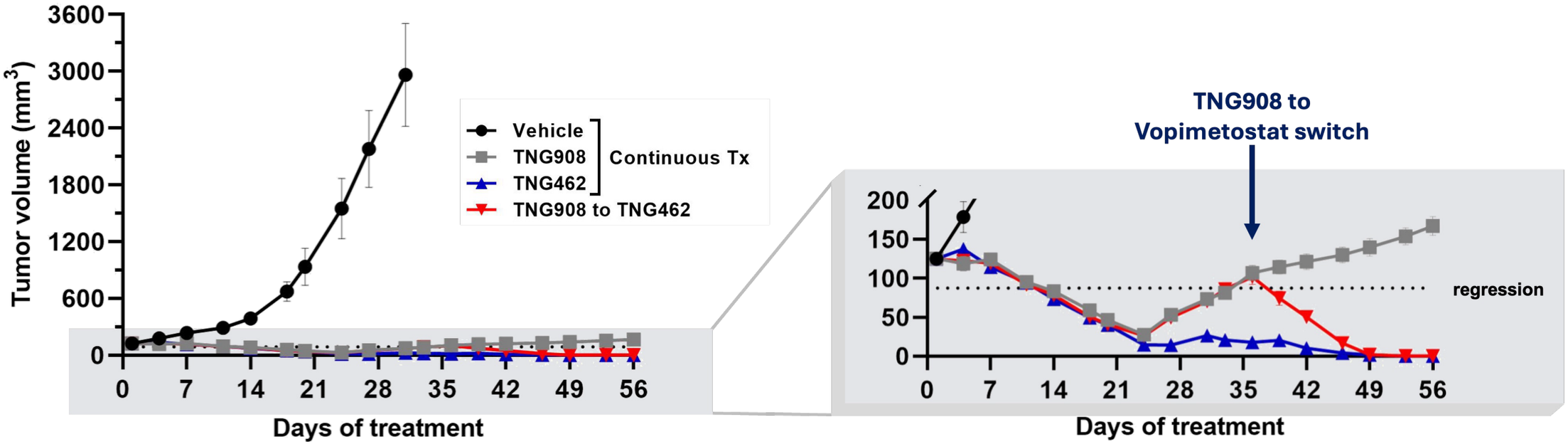
Cottrell KM, et al. J Med Chem **2025,** 68, 5097–5119

TANGO therapeutics

Vopimetostat re-sensitizes tumors with incomplete response to 1st generation MTA-cooperative PRMT5 inhibitor

OCI-LY19

MTAP-null DLBCL CDX



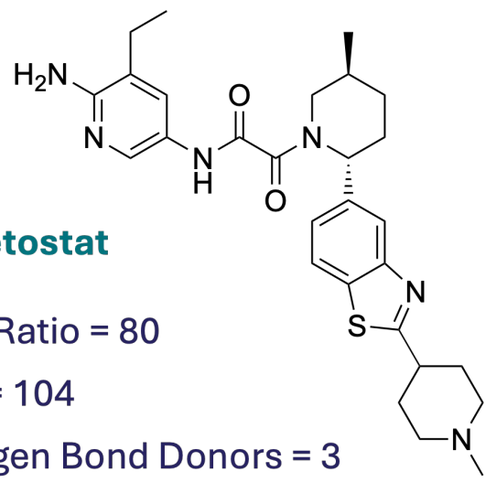
Cottrell KM, et al. J Med Chem **2025,** 68, 5097–5119

TNG456 is a brain-penetrant MTA-cooperative PRMT5 inhibitor

Typical molecular properties for CNS penetration
(MDR1 efflux < 3)

TPSA ≥ 40 and ≤ 90 Å^2, HBD ≤ 2,

cLogP ≤ 3, cLogD ≤ 2, pKa ≤ 8, MW ≤ 360



Vopimetostat

Efflux Ratio = 80

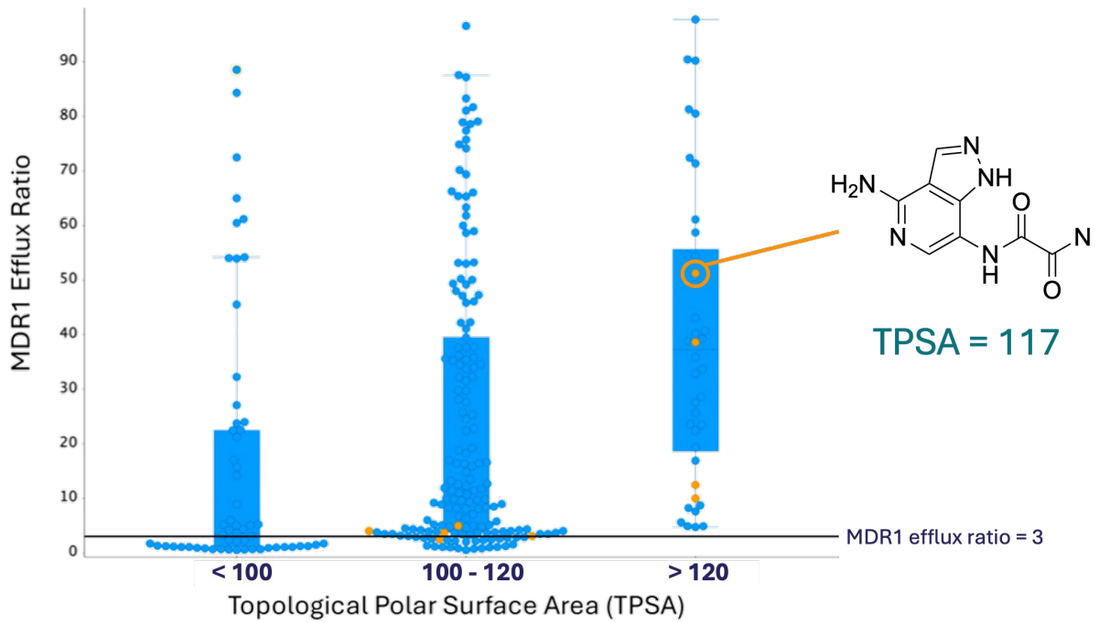
TPSA = 104

Hydrogen Bond Donors = 3

$LogD_{7.4}$ = 2.2

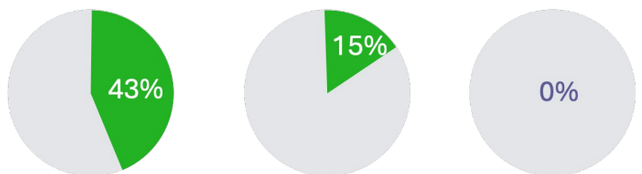
MW = 520

Oxamide analogs up to Vopimetostat

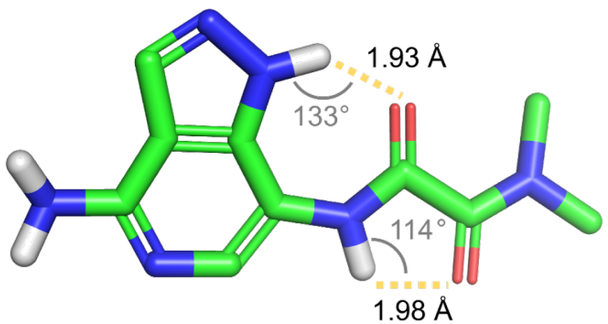


TPSA = 117

ER ≤ 3

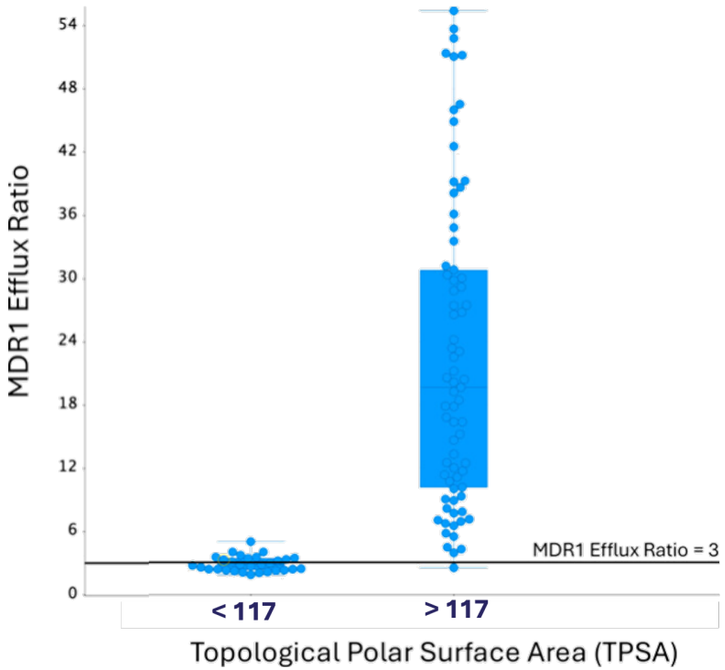


Polarity is ameliorated by IMHBs allowing for low efflux

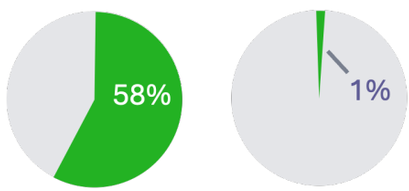


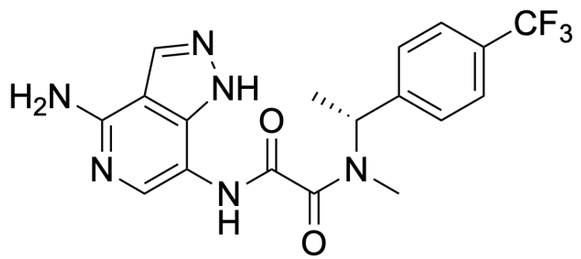
Lowest Energy calculation
Δ 2.6 kcal/mol

Aminopyrazolopyridine analogs



ER ≤ 3





TNG456

K_i < 0.002 nM
GI_{50} = 20 nM

- **50x MTAP-null selective in cells**
- **CNS penetrant**
- **Low efflux**
- **No CYP-mediated DDI**
- **Currently in clinical trials**

Cottrell, K. M. et al., J Med Chem, **2026**, 69, 12853-12869

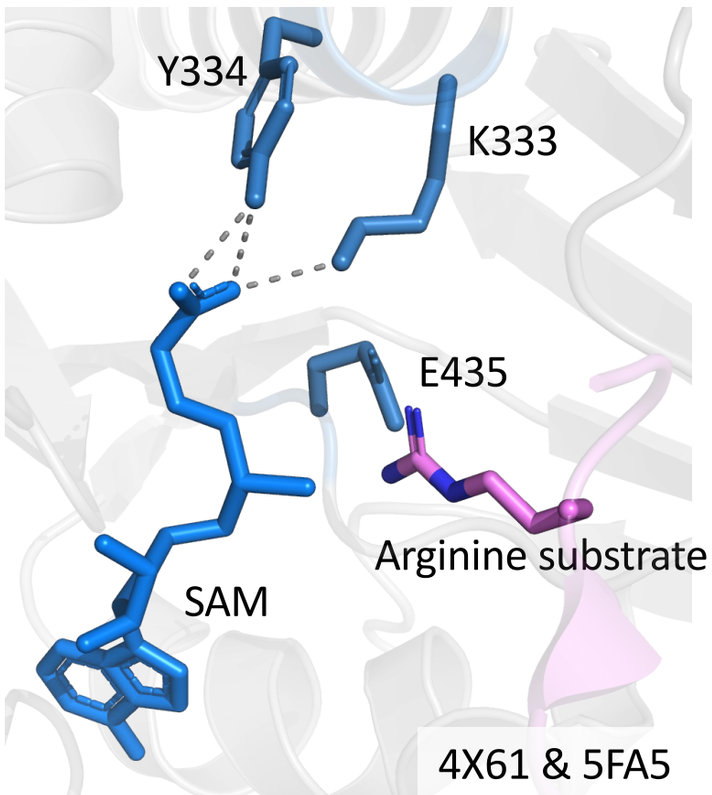
TANGO therapeutics

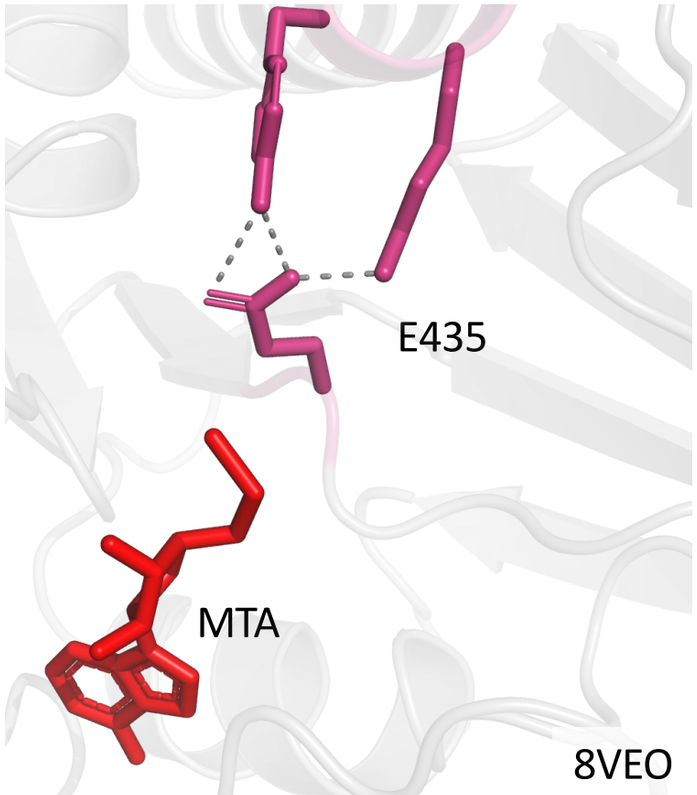
Glutamate 435 rotamer-lock is key to selective binding with MTA

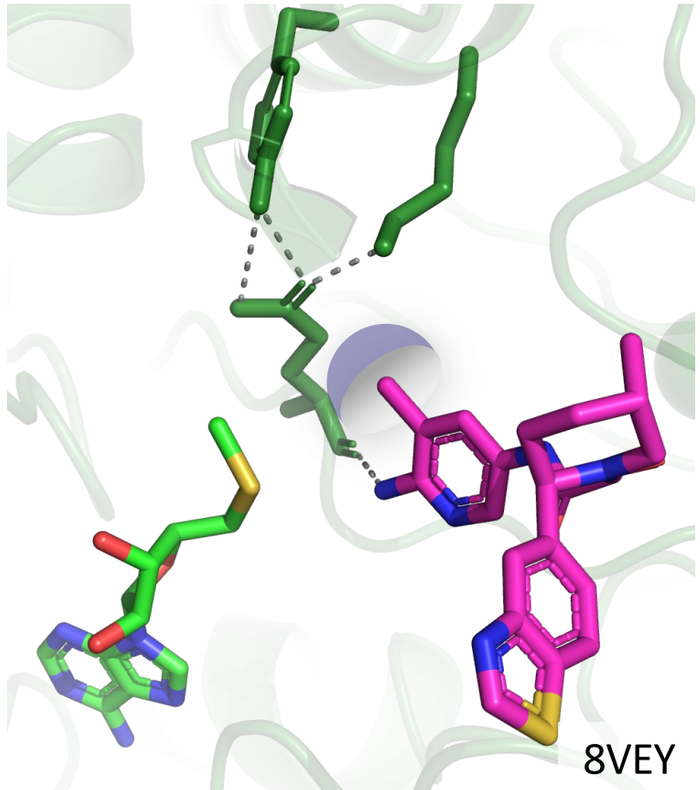
- SAM engages Y334/K333 in bioactive state
- E435 folded behind substrate

- E435 engages Y334/K333 sidechain when MTA is bound

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



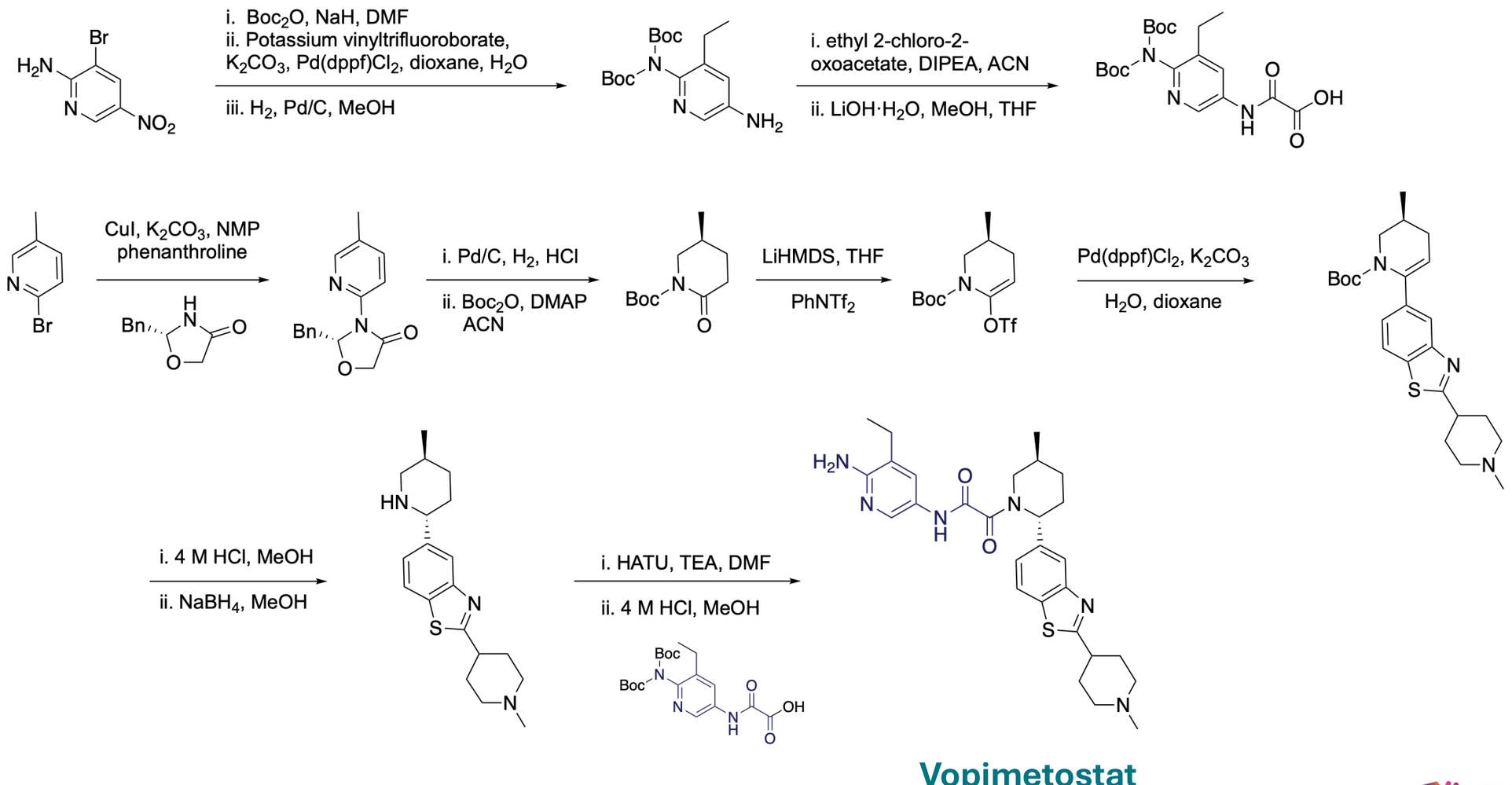




(a) Mavrakis, K. et al., Science **2016**. (b) Smith, C. et al., J Med Chem **2022**. (c) Cottrell, K. et al., J Med Chem **2024**, 67, 6064-6080. (d) Maxwell, J.; Cottrell, K.; Briggs, K. "Discovery of MTA-cooperative PRMT5 Inhibitors" in Epigenetic Drug Discovery, **2024**, Chapter 20, 623–650, Royal Society of Chemistry Books.

TANGO therapeutics

Chemical synthesis of Vopimetostat



Vopimetostat

Cottrell KM, et al. J Med Chem **2025,** 68, 5097–5119; Liang, C.; Li, H. Methods of preparing a PRMT5 inhibitor, WO/2025/260063

Summary

Highly potent, selective, and efficacious clinical compounds with first-in-class potential

High-throughput screening identified multiple chemical scaffolds

Oxamide scaffold enables highly efficient binding in a compact molecular assembly

Structure-guided design successful in establishing key protein-ligand interactions

Vopimetostat and TNG456 in clinical trials as monotherapy or in combination with other agents

Acknowledgements



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