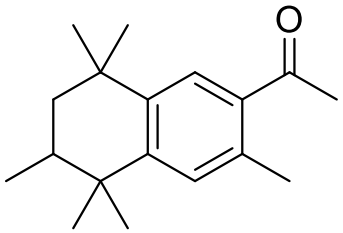
INTEGRATING PASS, LLM ANALYSIS, AND MOLECULAR DOCKING TO UNCOVER A TARGET SWITCH IN PYRIMIDINE DERIVATIVES

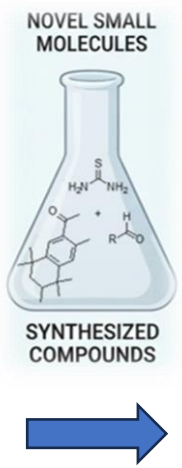
Tatyana Grigoreva,
St. Petersburg State Institute of Technology (Technical University), St. Petersburg, Russia

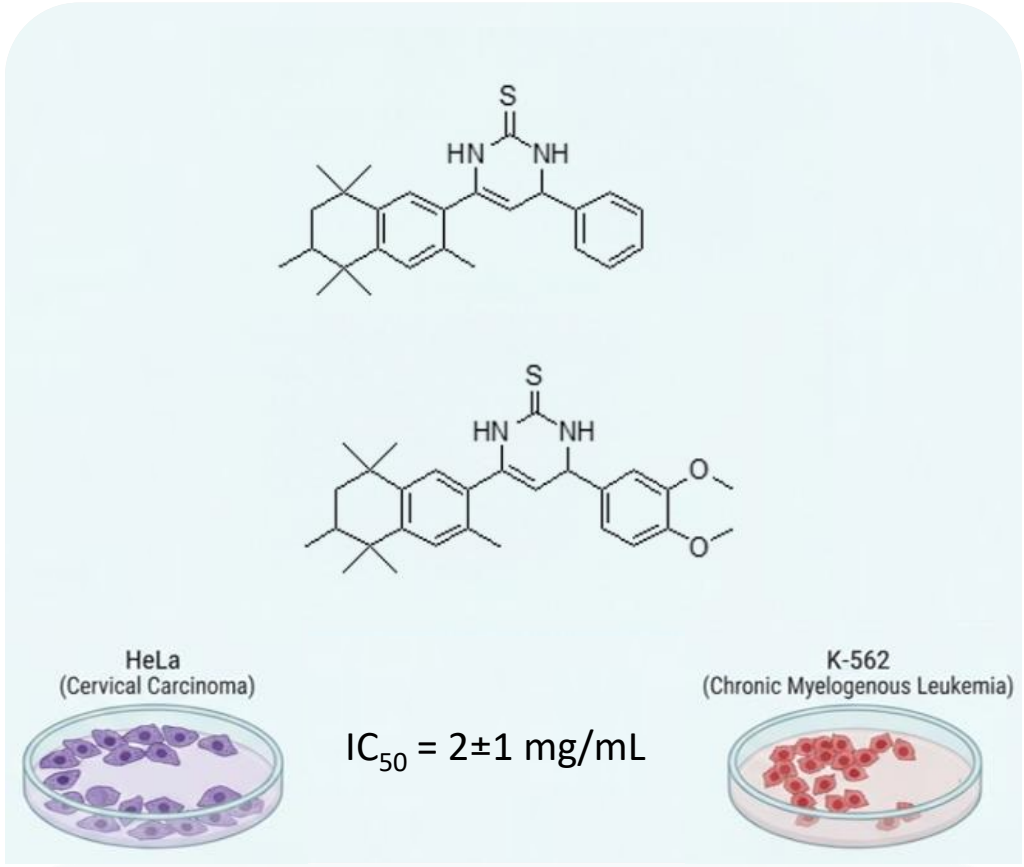
XXXII Symposium on Bioinformatics and Computer-Aided Drug Discovery (BCADD-2026)

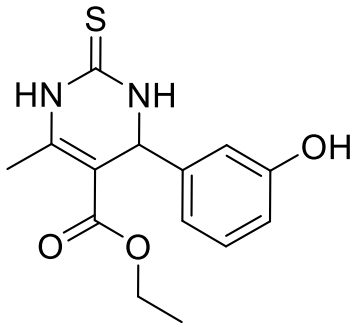
Background & Compound Classes



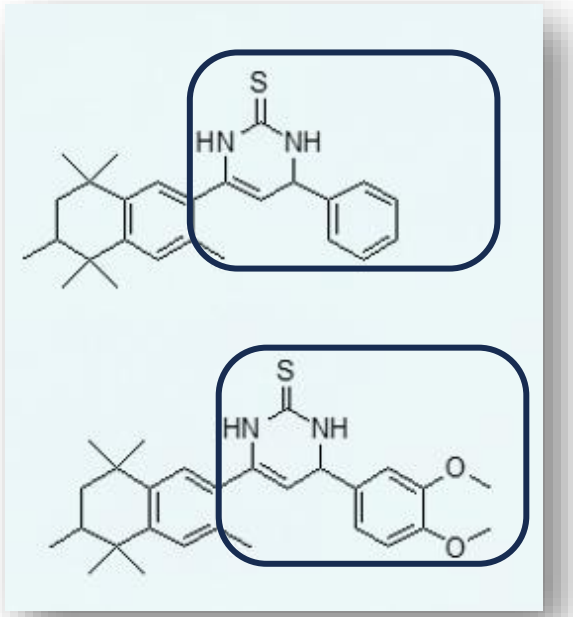
Tonalide

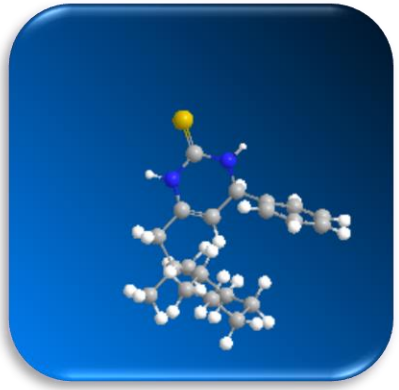


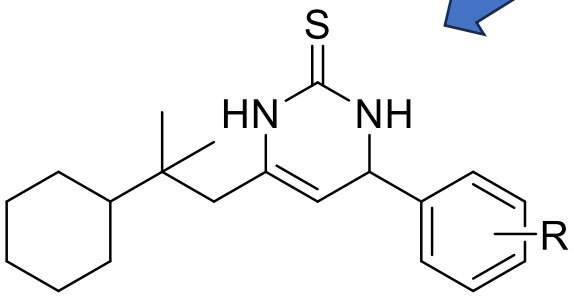




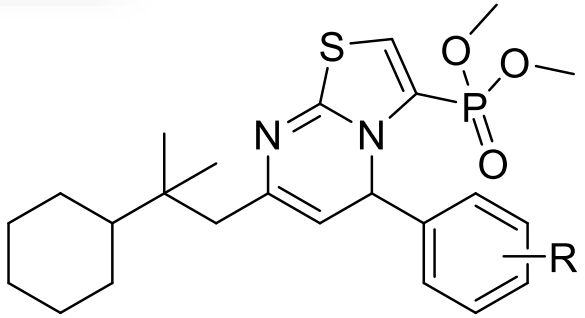
Monastrol
known inhibitor of
Kinesin Eg5







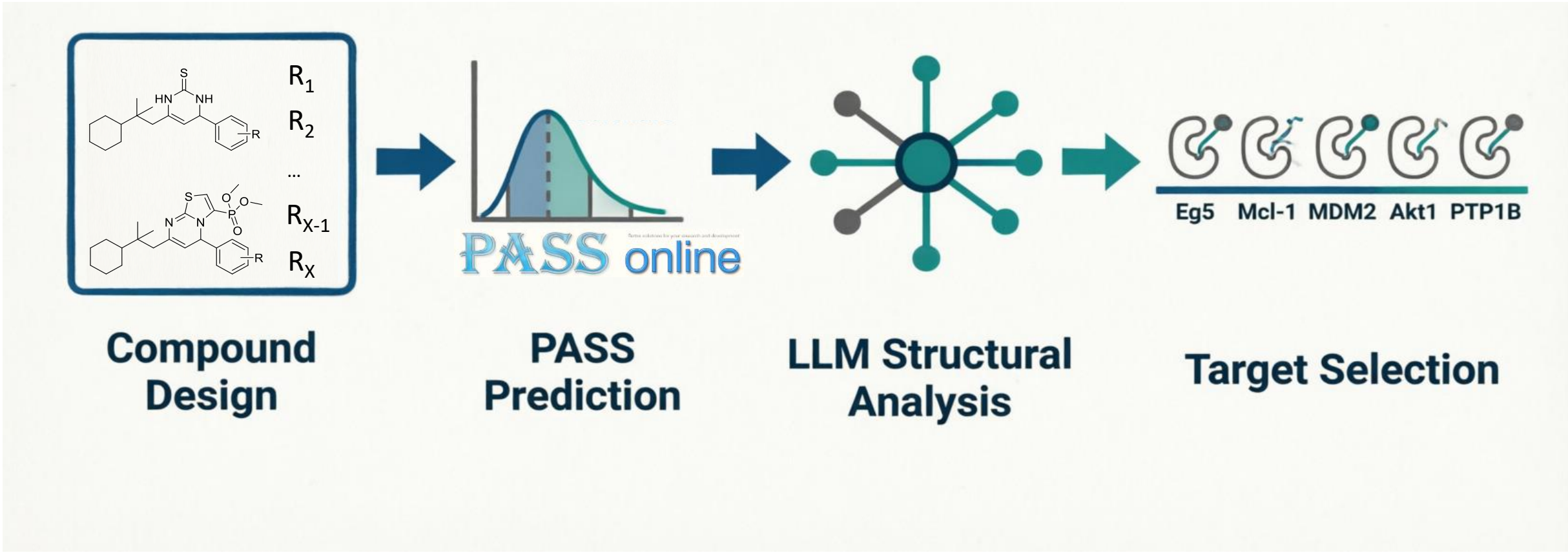
Dihydropyrimidinethiones
(DHPMTs)

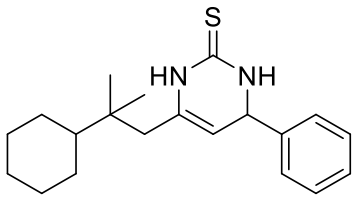


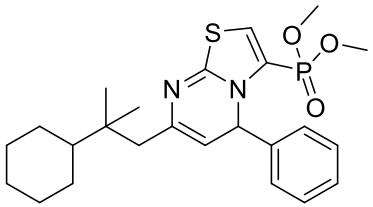
Thiazolopyrimidinephosphonates
(TZPMPs)



A Computational Drug Discovery Pipeline







0,655	0,004	**Antimitotic**
0,557	0,002	Protein kinase B inhibitor
0,548	0,004	**Antineoplastic (pancreatic cancer)**
0,588	0,054	*Phosphatase inhibitor*
0,527	0,022	Analgesic, non-opioid
0,573	0,083	Nicotinic alpha6beta3beta4alpha5 receptor antagonist
0,520	0,033	Analgesic
0,519	0,037	**Apoptosis agonist**
0,480	0,069	Antidyskinetic
0,507	0,129	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
0,415	0,043	Antiprotozoal (Leishmania)
0,448	0,075	Chloride peroxidase inhibitor
0,461	0,091	Nicotinic alpha2beta2 receptor antagonist
0,350	0,004	Histone deacetylase SIRT1 inhibitor
0,480	0,160	Ubiquinol-cytochrome-c reductase inhibitor
0,359	0,046	Vanilloid 1 agonist
0,430	0,123	Acute neurologic disorders treatment
0,408	0,101	Antineoplastic
0,450	0,149	CYP2J substrate
0,304	0,005	Histone deacetylase class III inhibitor
0,438	0,140	Kidney function stimulant
0,409	0,114	Ovulation inhibitor
0,452	0,161	CYP2H substrate
0,308	0,022	**ATPase stimulant**
0,352	0,075	CYP2C19 inducer

0,688	0,015	*Phosphatase inhibitor*
0,554	0,006	**Antimitotic**
0,476	0,024	Antihypertensive
0,426	0,012	**Antineoplastic (pancreatic cancer)**
0,413	0,007	Bone formation stimulant
0,409	0,038	Calcium regulator
0,352	0,003	Protein kinase B inhibitor
0,344	0,034	Bone diseases treatment
0,308	0,014	Antischistosomal
0,270	0,015	**Antineoplastic (bone cancer)**
0,430	0,183	CYP2H substrate
0,288	0,057	Undecaprenyl-phosphate mannosyltransferase inhibitor
0,255	0,067	Amyotrophic lateral sclerosis treatment
0,276	0,128	Cholesterol antagonist
0,214	0,070	Phospholipase A1 inhibitor
0,274	0,131	Vanilloid 1 agonist
0,299	0,161	Antiinflammatory
0,318	0,187	Neurotransmitter uptake inhibitor

Promising Targets

PASS → Qwen3.7-Plus

🎯 **Priority Targets (PASS & Antitumor Rationale)**:

Kinesin-like protein 1 (Eg5) & Tubulin:
Eg5 inhibition → metaphase arrest & tumor cell apoptosis.
β-tubulin: control target.

Protein Kinase B (Akt / PKB):
Key node in the PI3K/Akt/mTOR pathway that transduces extracellular growth and metabolic signals to regulate fundamental cellular processes, including growth and proliferation.

CDC25 / SHP2:
Highly relevant as "Phosphatase inhibitors" in an antimitotic context.

Apoptosis Targets (Bcl-2 / Bcl-xL / IAPs):
Act as Apoptosis agonists. Binding to Bcl-2 or Bcl-xL suggests BH3-domain mimicry, explaining pro-apoptotic effects.

🔬 **Promising Alternative Targets**

SIRT1 / SIRT2
Tankyrase (TNKS1/2)
Pin1

Integration of PASS & Structural Analysis

PASS

SMILES

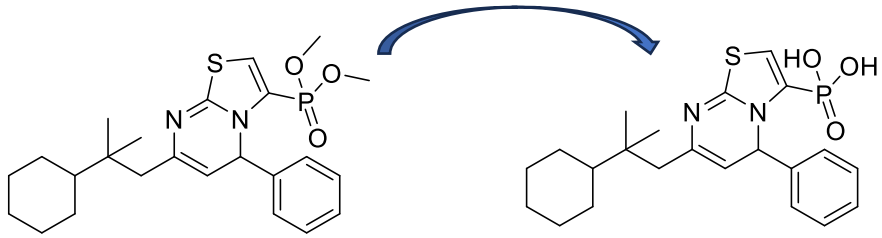
Qwen

Qwen3.7-Plus

🎯 **Eg5 (KIF11)**
Antimitotic activity / Kinesin antagonist
PDB: 2HHD or 3HQQ

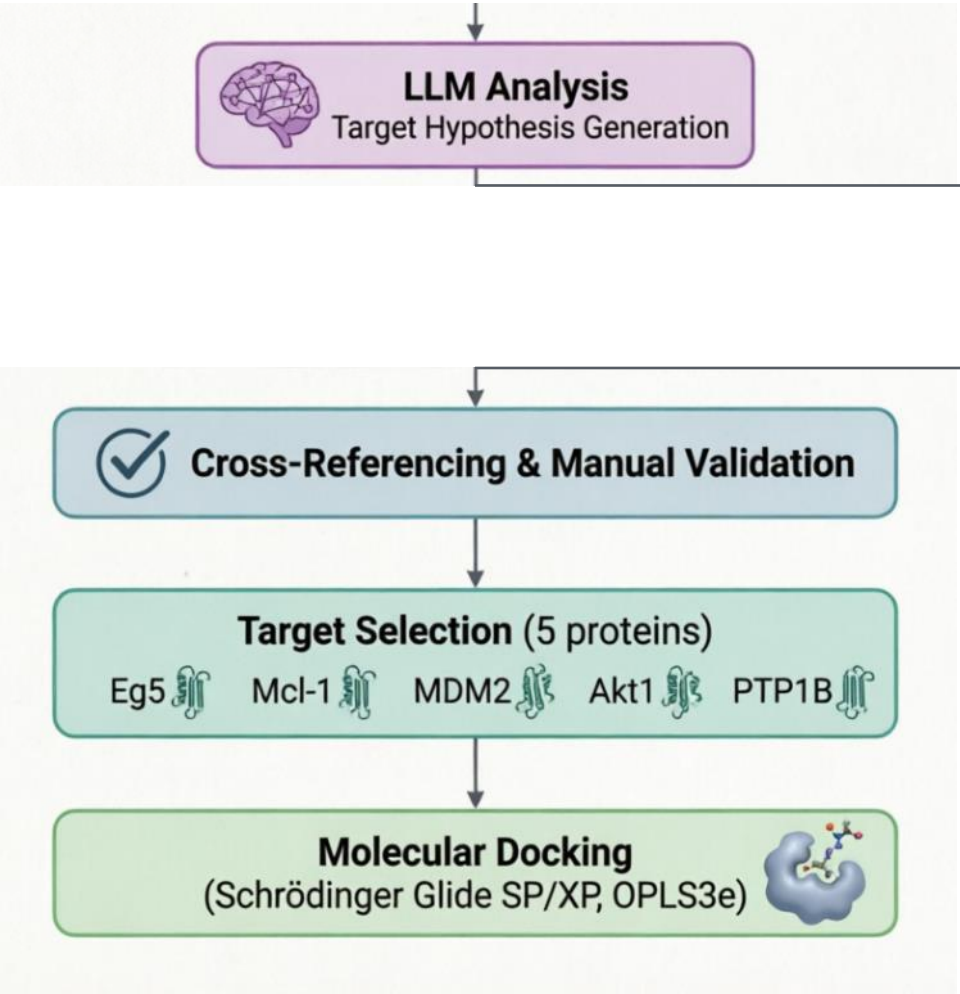
🎯 **Akt1 (PKB)**
Kinase inhibitor
PDB: 3O96 or 3CQU

🎯 **CDC25B / PTP1B**
Phosphatase inhibitor
1CWR or 1T4N



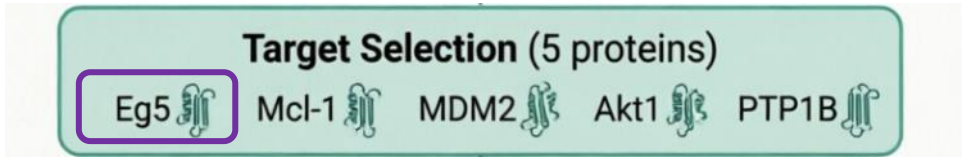
•*Note: Dimethyl esters may undergo hydrolysis in vivo.*

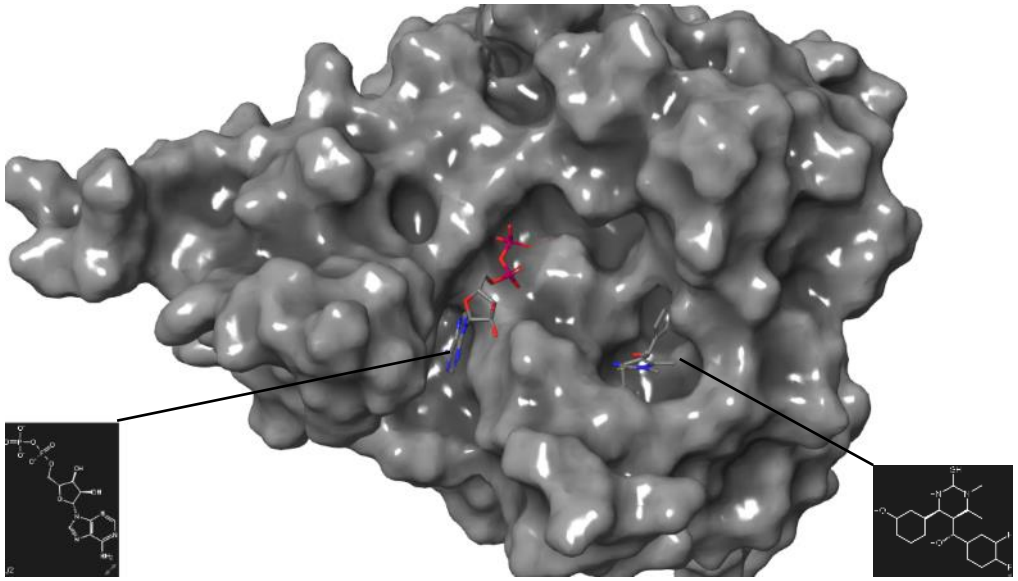
Apoptosis Target Analysis: Hypotheses



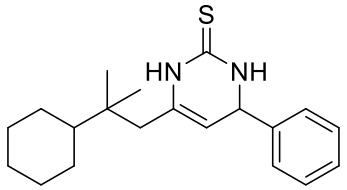
Hypothesis A (Mitochondrial pathway):
Compounds (especially with bulky cyclohexyl tails) act as **BH3-mimetics**, inhibiting Bcl-2, Bcl-xL, or Mcl-1.

Hypothesis B (p53 pathway):
Compounds act as **MDM2 inhibitors**, stabilizing p53 by occupying its hydrophobic pockets.

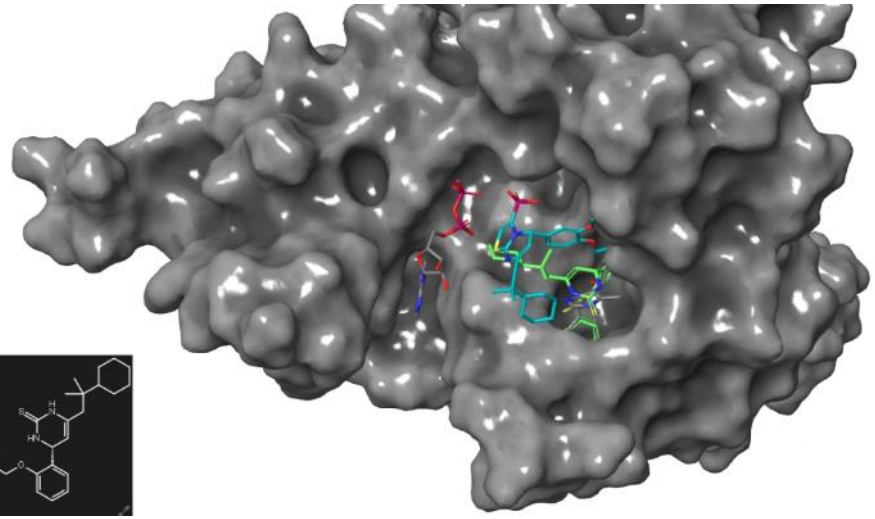




2X7E:
Crystal structure of human kinesin Eg5 in complex with (R)-fluorastrol

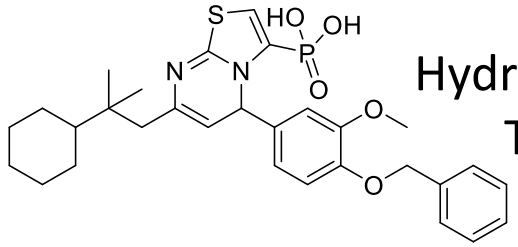


DHPMT

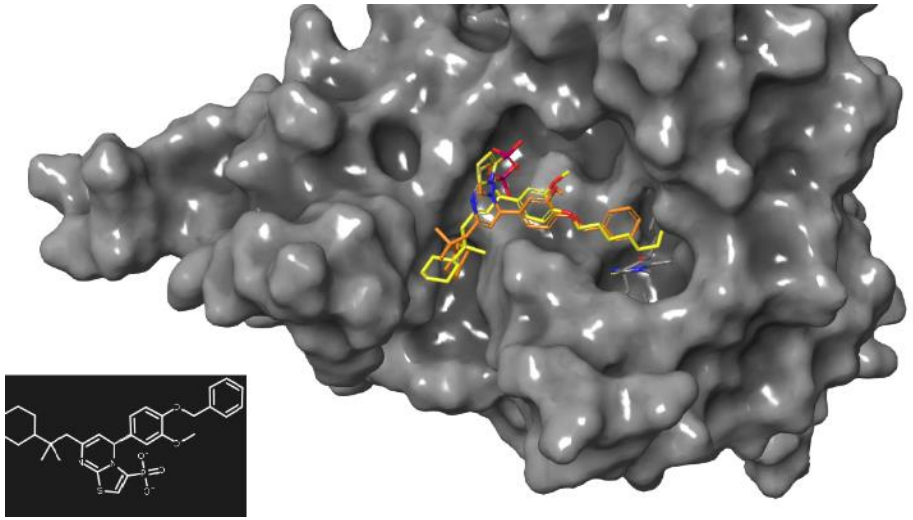


-6.65
kcal/mol

ATP pocket contains positively charged residues (Lys103, Arg119). Negatively charged phosphonate forms salt bridges.

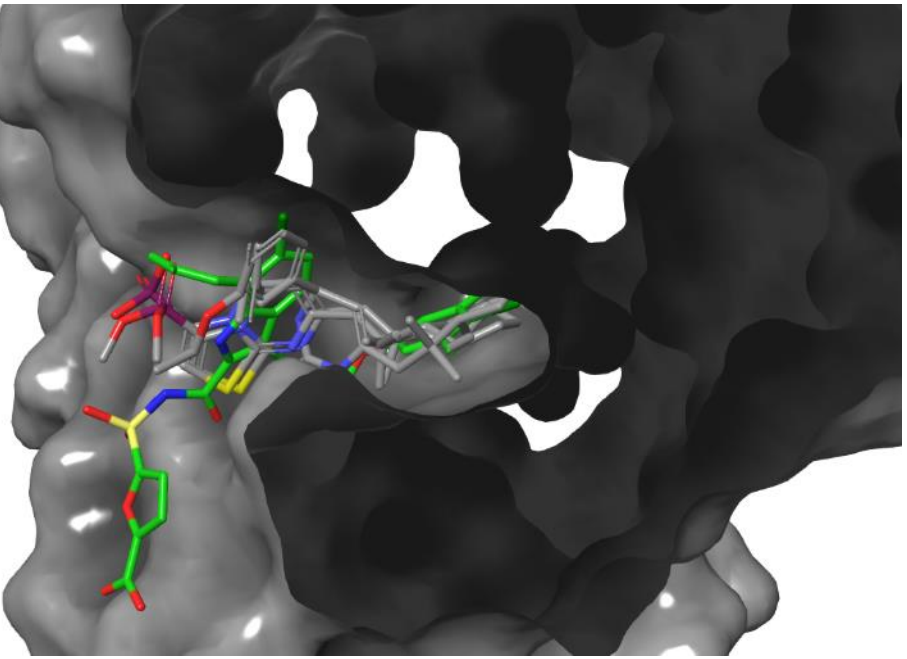


Hydrolyzed
TZPMP



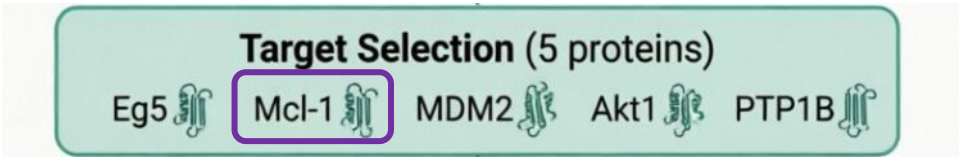
-9.38*
kcal/mol

* Nonhydrolyzed TZPMP = -6.65 kcal/mol



5FDR:
Mcl-1 complexed with small molecule inhibitor

Mcl-1 contains a deep hydrophobic groove that binds the BH3 domain of proapoptotic proteins (e.g., Bax, Bak).



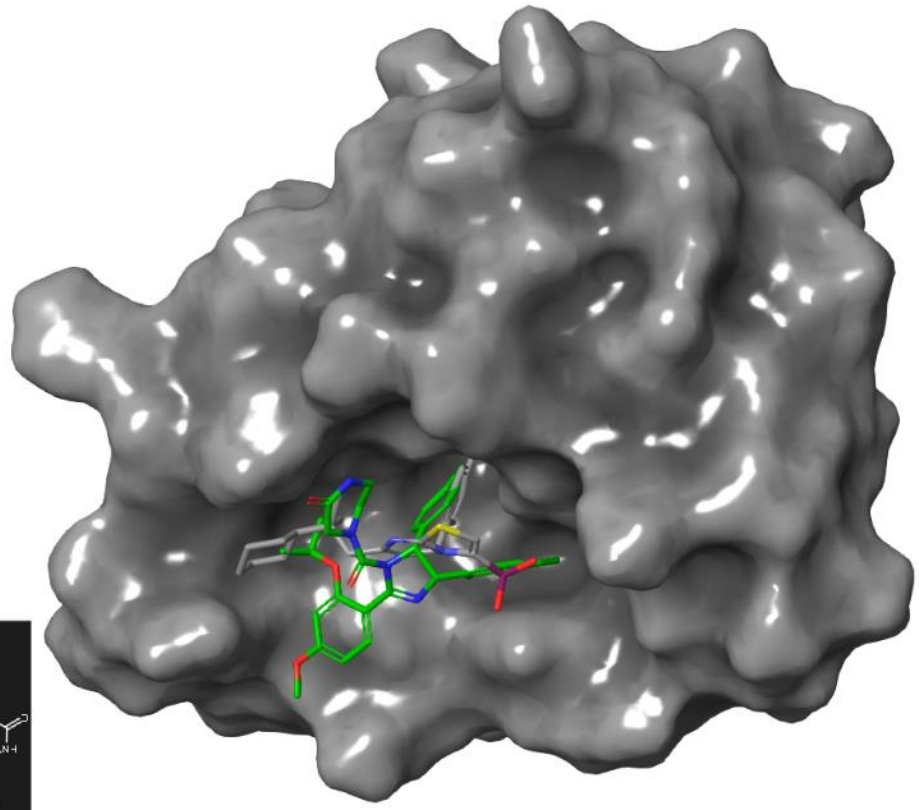
DHPMT: -6.3 ÷ **-8.5** kcal/mol

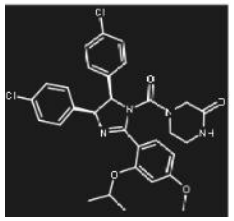
TZPMP: -5.8 до **-7.8** kcal/mol

Hydrolyzed TZPMP: -6.2 до **-8.2** kcal/mol

LC3: **-9.3** kcal/mol

Bulky, lipophilic 2-cyclohexyl-2-methylpropyl group + aromatic rings act as an ideal "plug".
Phosphonate group does not interfere; may form weak edge electrostatic contacts.





4HG7:
Crystal Structure of an MDM2/Nutlin-3a complex



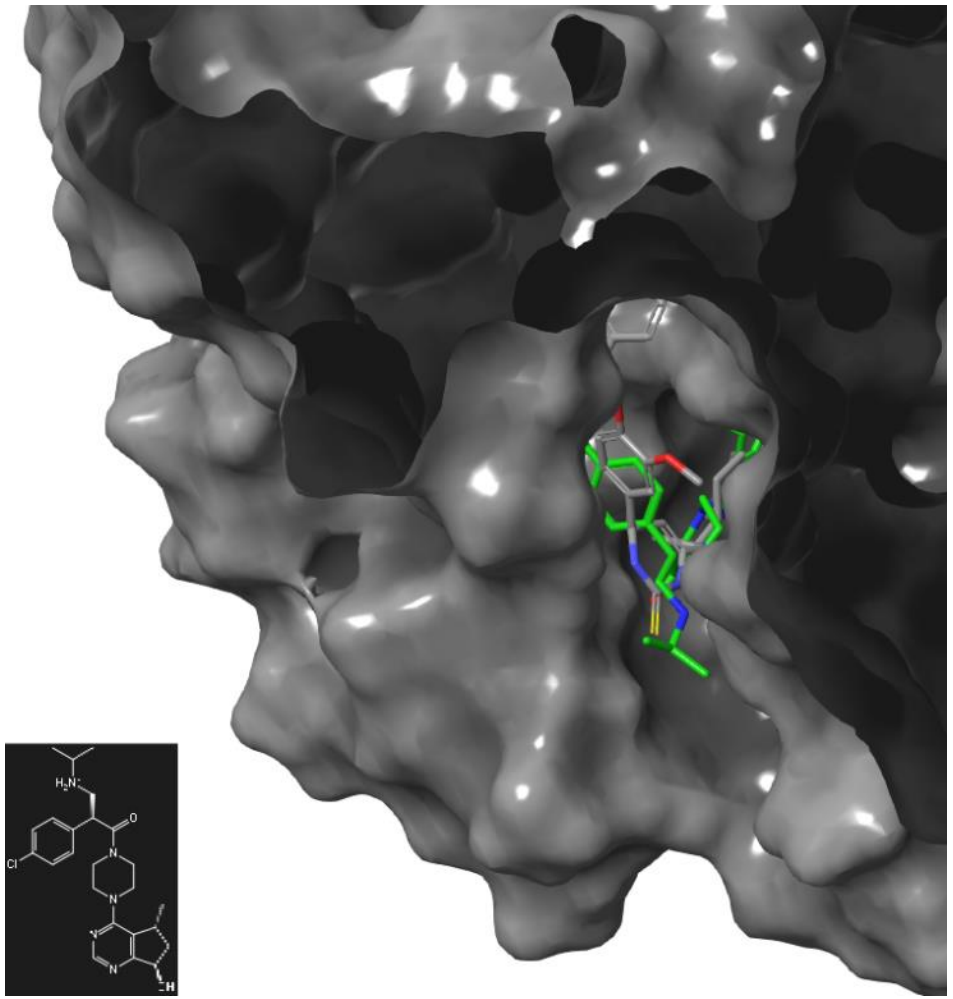
DHPMT: -4.5 ÷ -5.5 kcal/mol

TZPMP: - 4.1 ÷ -6.7 kcal/mol

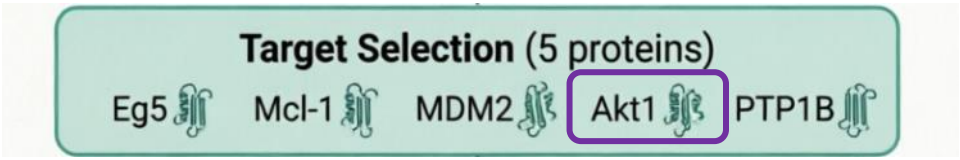
Hydrolyzed TZPMP: 6.2 ÷ **-7.8** kcal/mol

Nutlin-3a: **-7.5** kcal/mol

Phosphonate group forms favorable electrostatic/H-bond interactions (e.g., with His96, Gln59).



4EKL:
Akt1 with GDC0068



DHPMT: max -5.5 kcal/mol

TZPMP: max -5.3 kcal/mol

Hydrolyzed TZPMP: max -4.6 kcal/mol

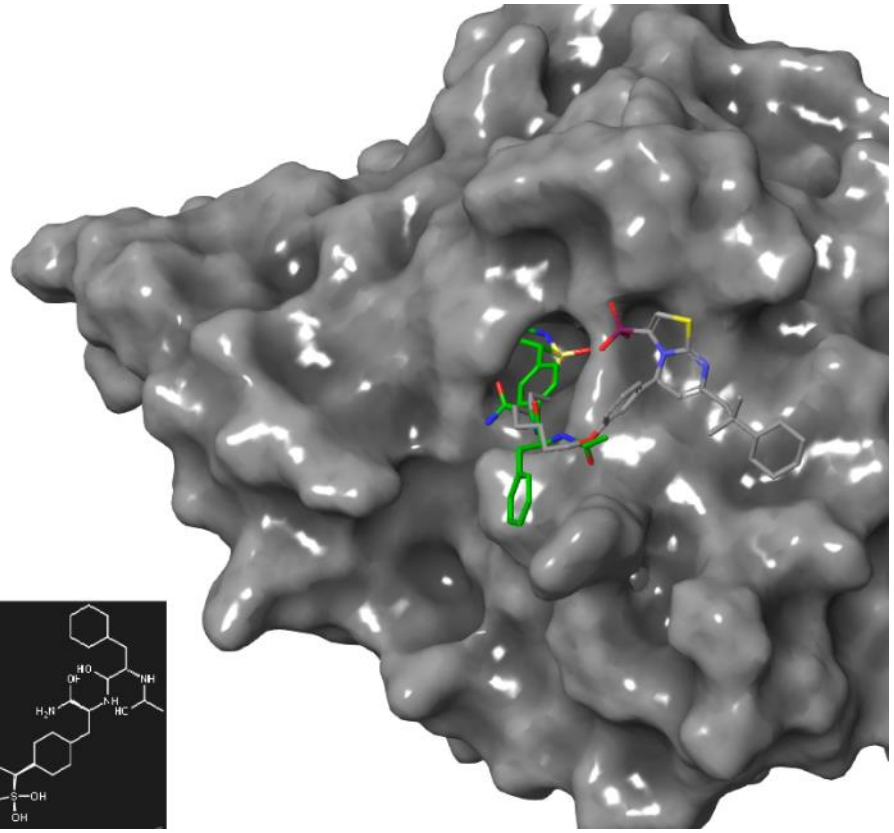
GDC0068: **-6.7** kcal/mol

A built-in steric filter prevents penetration into narrow catalytic tunnels.

Compounds are **NOT** competitive catalytic site inhibitors

↓

?Potential allosteric inhibitors?



2CM7:
Structural Basis for Inhibition of Protein Tyrosine Phosphatase 1B by Isothiazolidinone Heterocyclic Phosphonate Mimetics



DHPMT: max -3.4 kcal/mol

TZPMP: max -3.8 kcal/mol

Hydrolyzed TZPMP: max -5.0 kcal/mol

IZD: **-8.5** kcal/mol

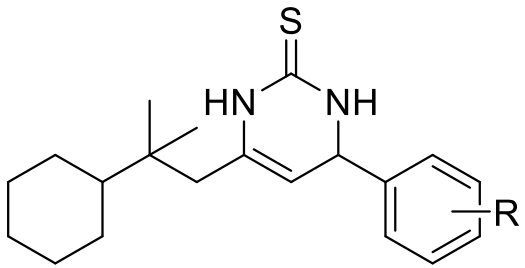
A built-in steric filter prevents penetration into narrow catalytic tunnels.

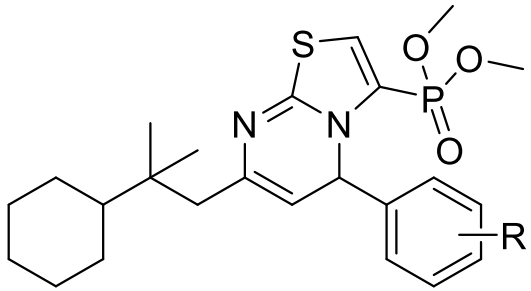
Compounds are **NOT** competitive catalytic site inhibitors

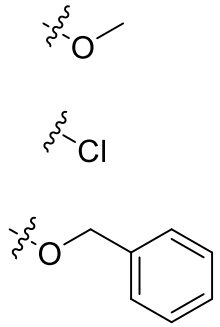
↓

?Potential allosteric inhibitors?

Molecular Docking Insights

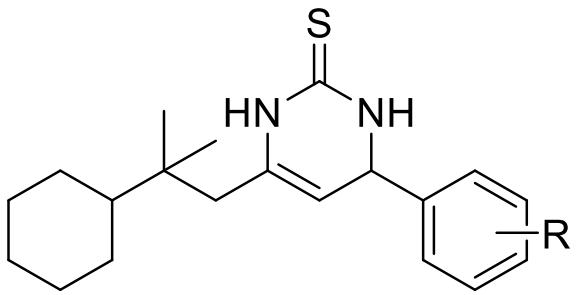


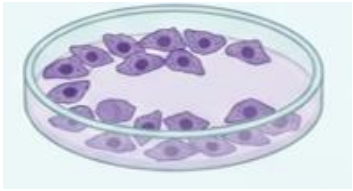


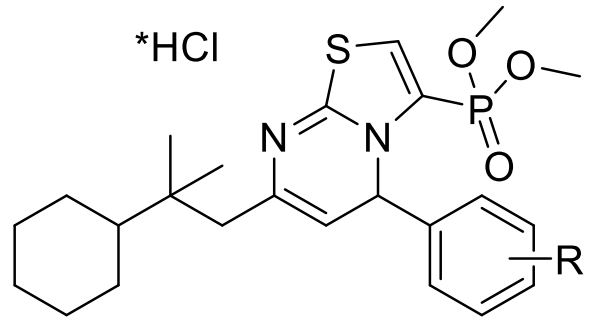


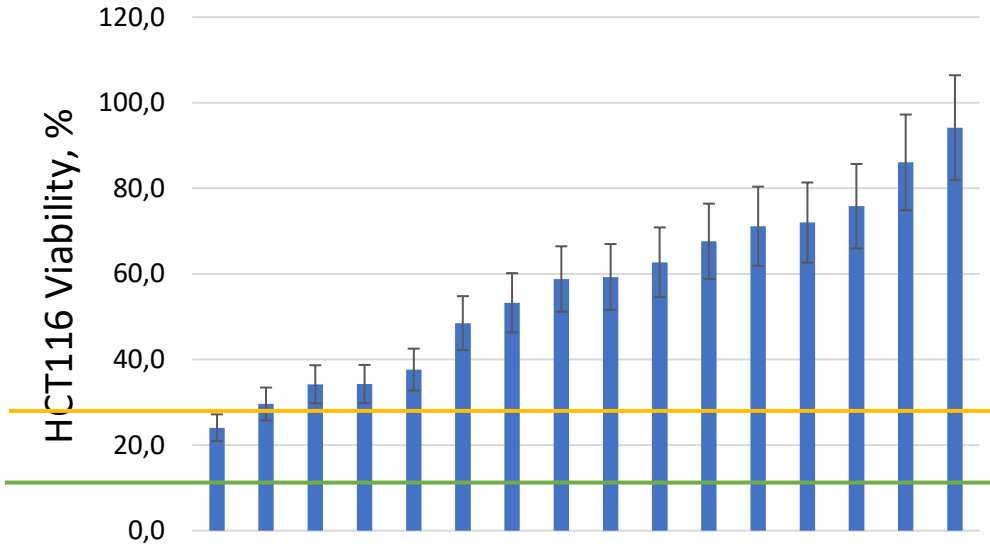
BH3-mimetics	✓	✓	Lipophilic tail + aromatic rings plug the BH3 groove
MDM2 inhibitors	✗	✓	Aromatic rings fill hydrophobic pockets + phosphonate anchors via electrostatic interactions
Eg5 inhibitors	✗	✓✓	Allosteric binding + phosphonate salt bridges in ATP-pocket
Akt1	✗	✗	Built-in steric filter prevents penetration into the narrow catalytic tunnels
PTP1B	✗	✗	

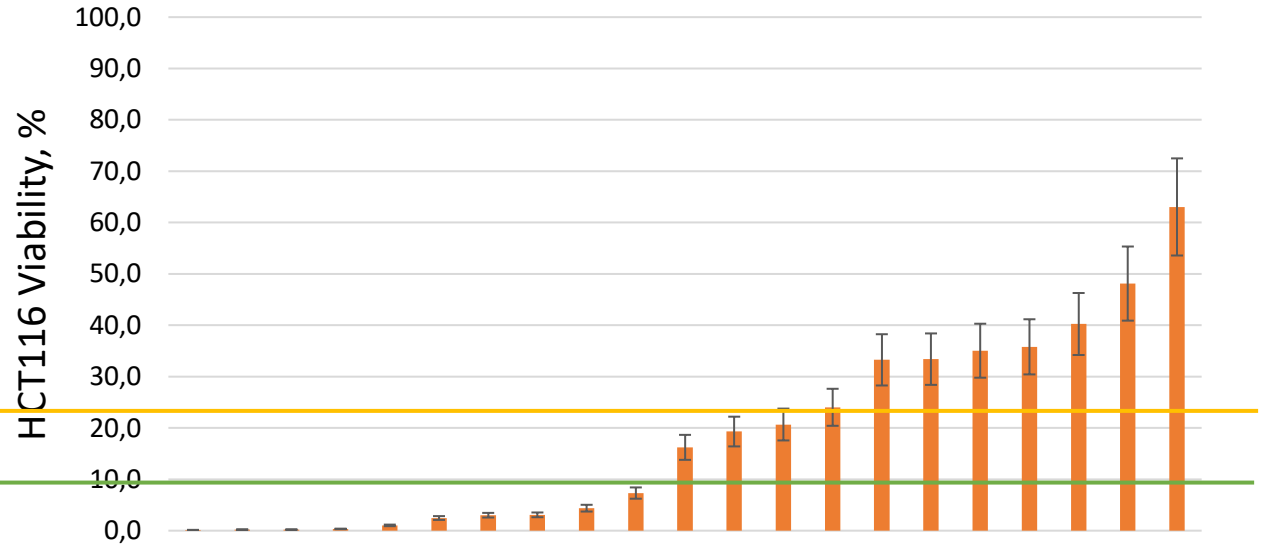
In Vitro Cytotoxicity (MTT Assay)





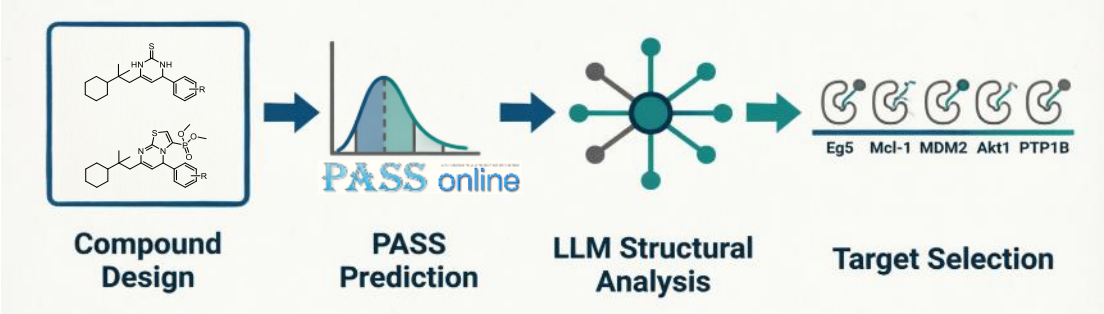


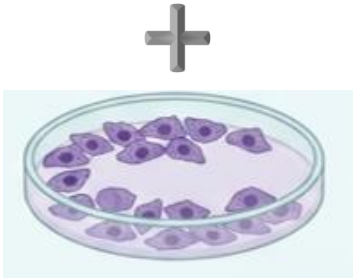


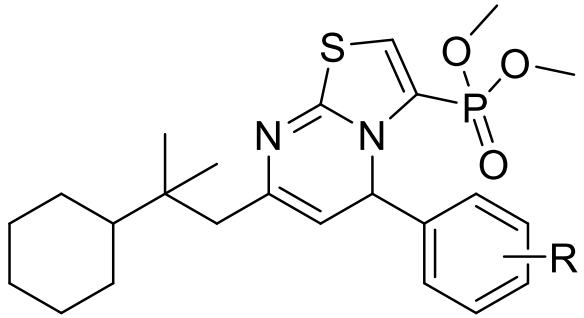


10 µM concentration, 48 h incubation, HCT116 (colon cancer) cell line

Conclusion







Thiazolopyrimidinephosphonates
are a highly promising class of antitumor agents

Primary Mechanism:
Eg5 inhibition (both allosteric and ATP-competitive binding)
→ mitotic catastrophe and apoptosis

Secondary Mechanisms:
Reactivation of pro-apoptotic proteins via MDM2 and BH3-receptors (Bcl-2/Mcl-1) inhibition

Saint-Petersburg State Institute of Technology

Thank you!

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https://vk.com/molpharm