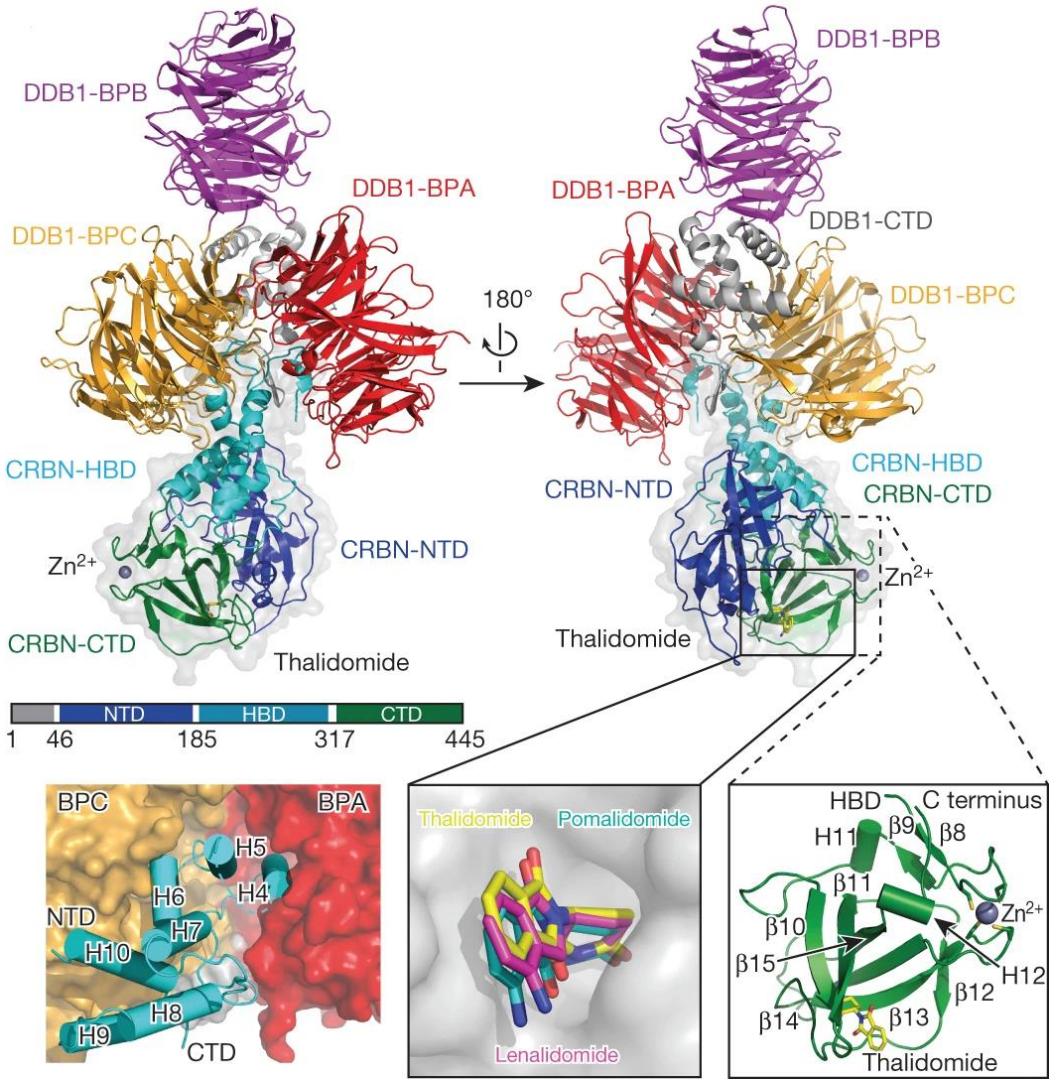
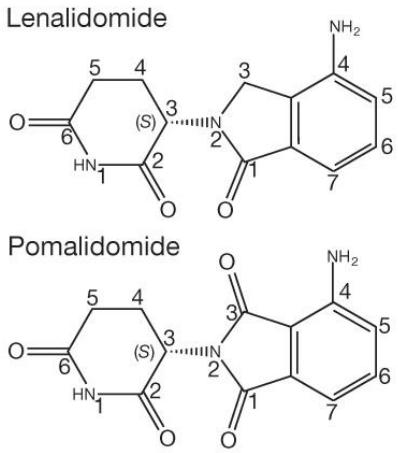
Discovery of CRBN-Dependent WEE1 Molecular Glue Degraders from a Multicomponent Combinatorial Library

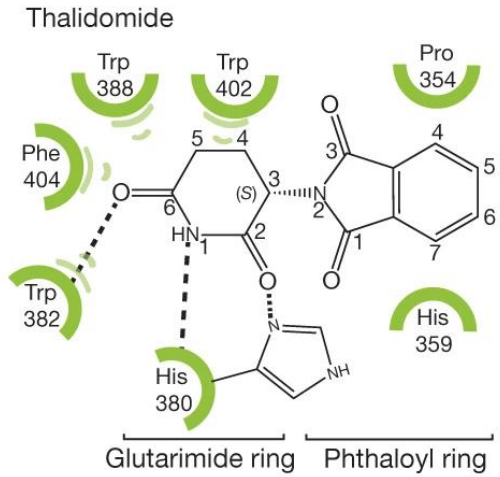
Qi Dai

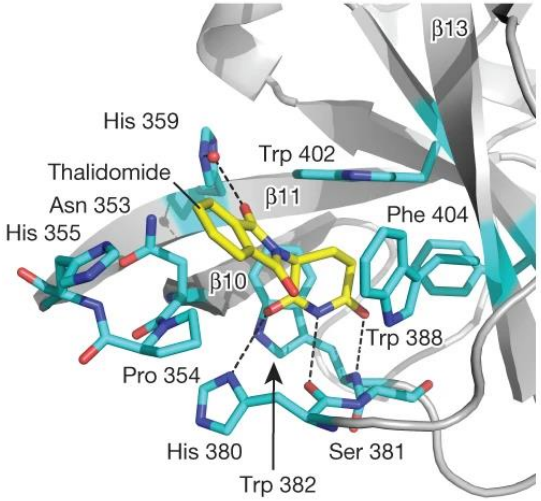
18/01/2025

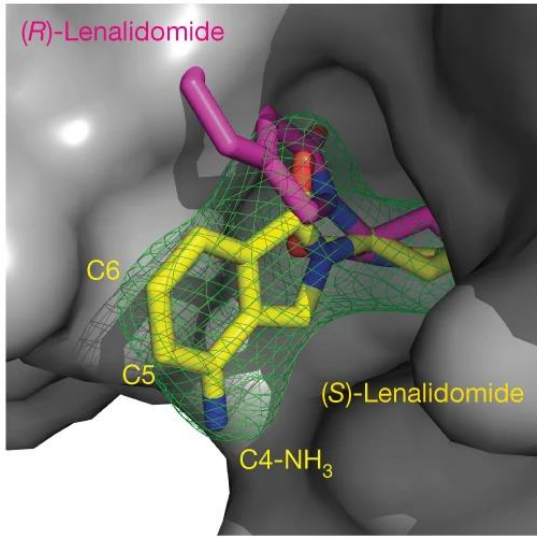
Structure of the DDB1-CRBN E3 Ubiquitin Ligase Bound to Thalidomide





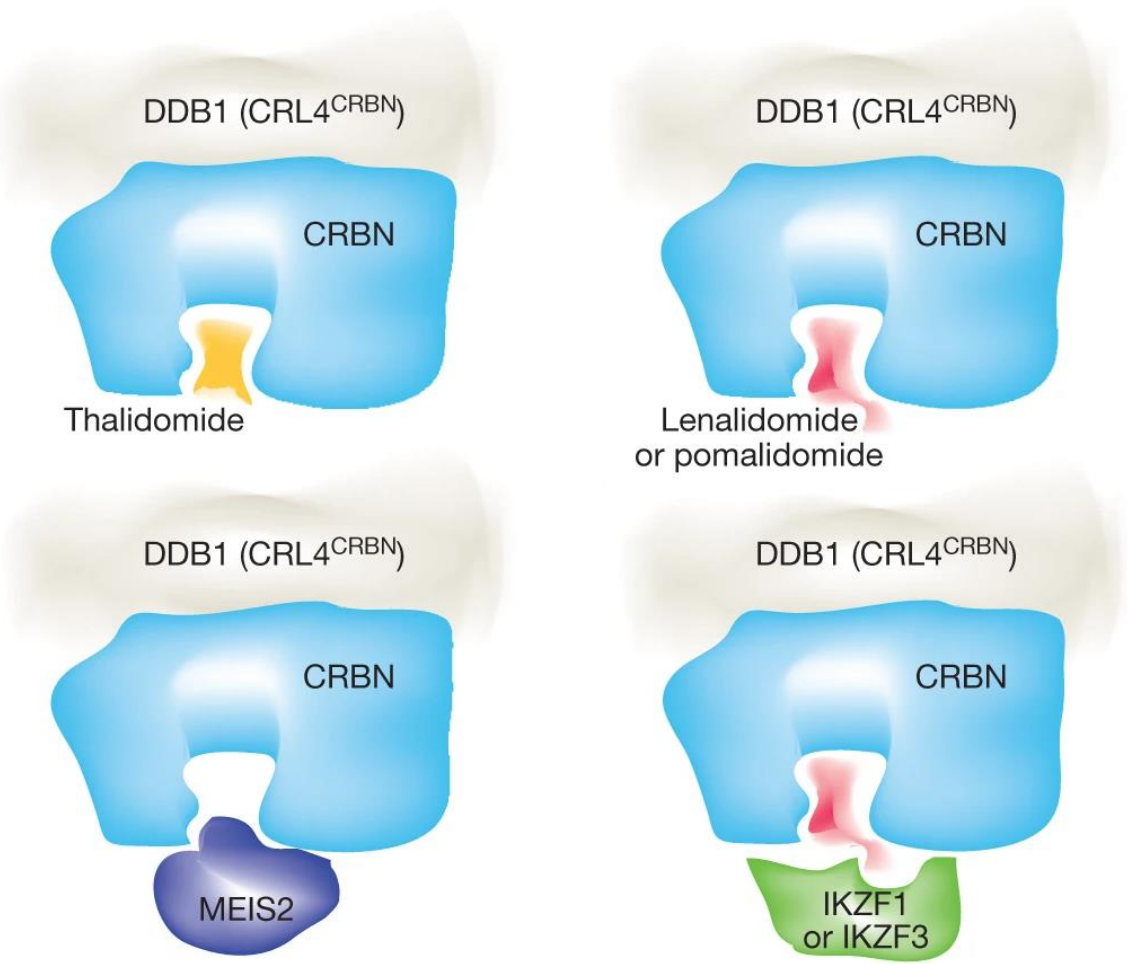


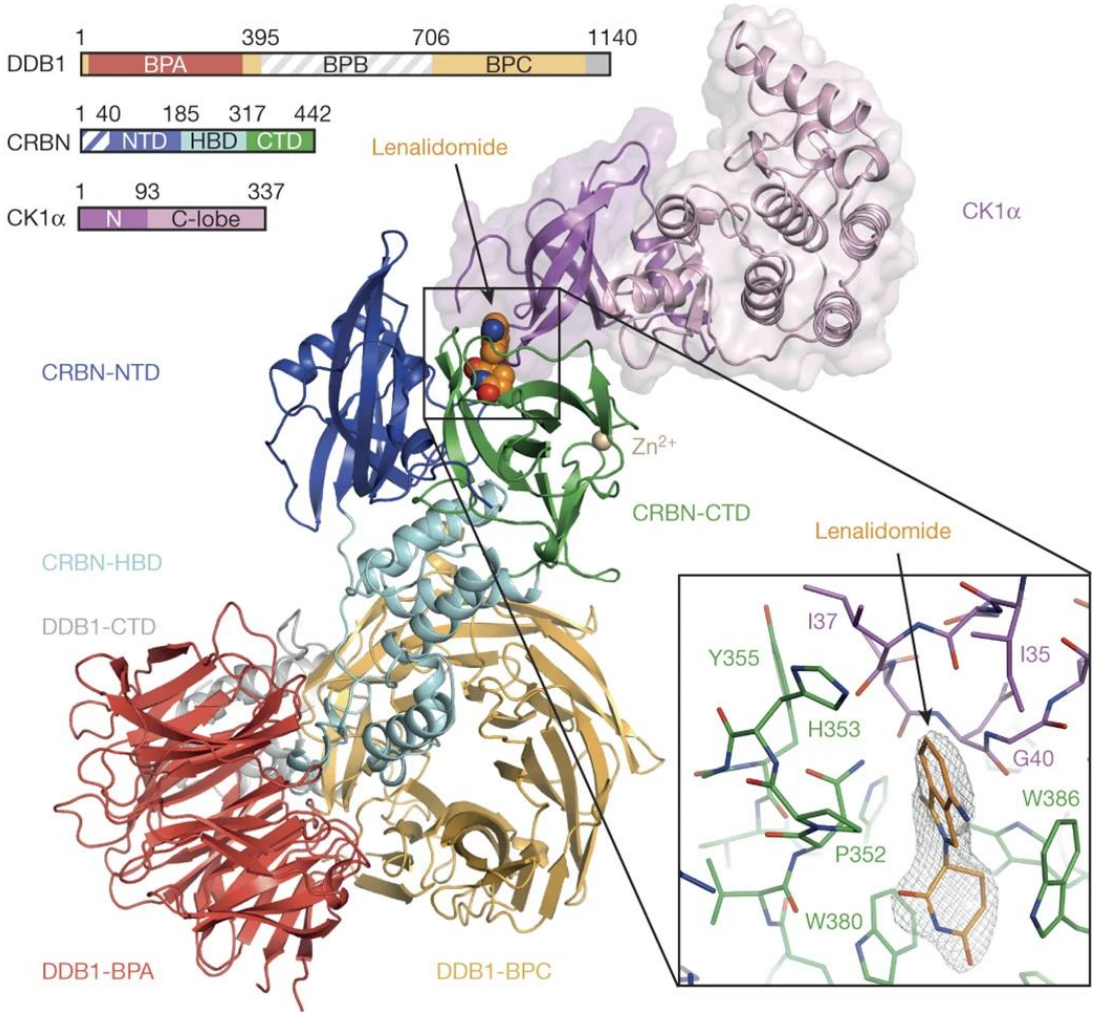




Nature. **2014** Aug 7;512(7512):49-53.

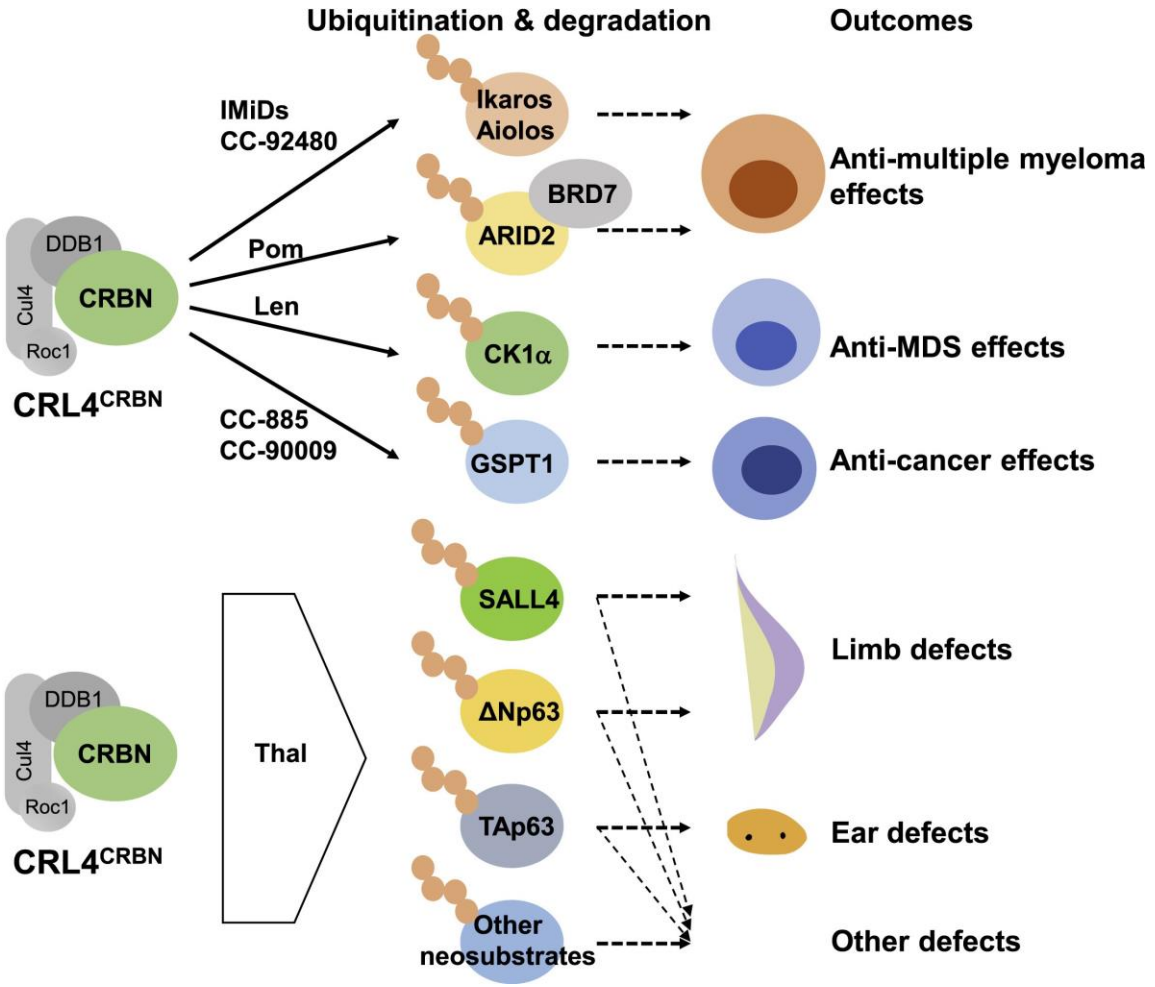
IMiDs Binding to Cereblon





Nature. **2016** Apr 7;532(7597):127-30.

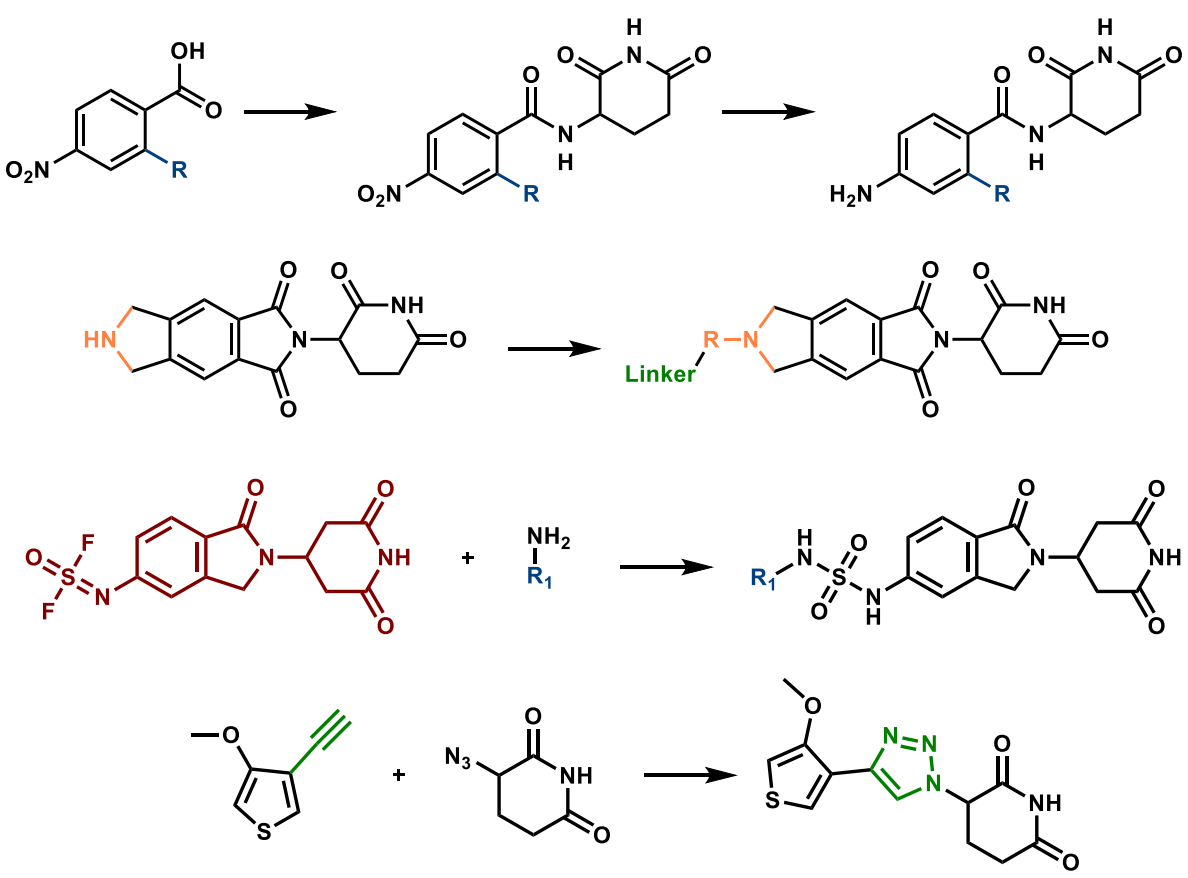
CRBN Substrates



Ikaros	✓	✓	Kronke et al., 2014; Lu et al., 2014; Gandhi et al., 2014; Sievers et al., 2018a; 2018b
Aiolos	✓	✓	Kronke et al., 2014; Lu et al., 2014; Gandhi et al., 2014
CK1α	✓	✓	Kronke et al., 2015; Petzold et al., 2016
GSPT1	✓	✓	Matyskiela et al., 2016; Sperling et al., 2019
ZFP91	✓		An et al., 2017; Sievers et al., 2018a, 2018b
SALL4	✓	✓	Donovan et al., 2018; Matyskiela et al., 2018a, 2018b
p63			Asatsuma-Okumura et al., 2019a, 2019b
Aromatase			Tochigi et al., 2020
ARID2			Yamamoto et al., 2020
BK channel	✓		Liu et al., 2014; Tao et al., 2018
MEIS2	✓		Fischer et al., 2014; Tao et al., 2018
CLC-1	✓		Chen et al., 2015; Tao et al., 2018
CLC-2			Fu et al., 2020
AMPKα			Kwon et al., 2019
Glutamine synthetase			Nguyen et al., 2016

Cell Chem Biol. **2021** Jul 15;28(7):987-999.

Design and Synthesis of Novel Cereblon Binders

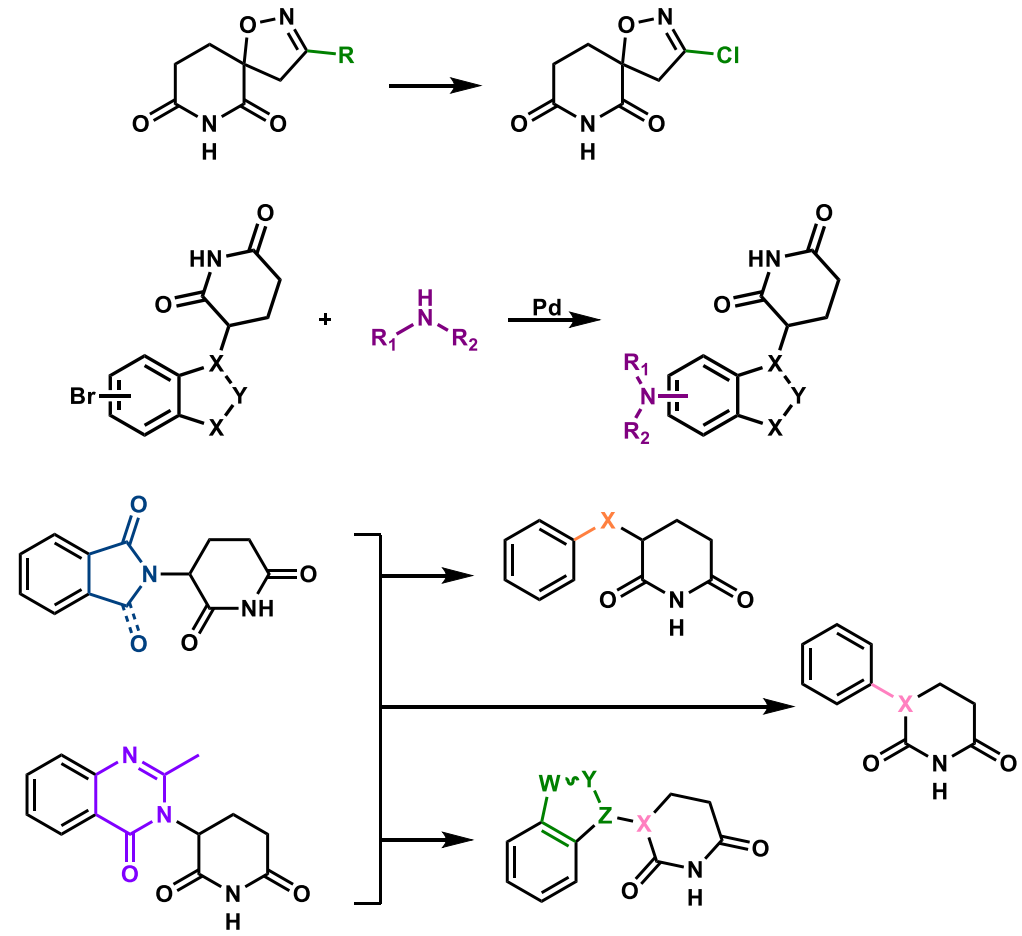


J Med Chem. **2023** Nov 9;66(21):14513-14543.

J Med Chem. **2023** Sep 14;66(17):12559-12585.

Bioorg Med Chem. **2024** Apr 15;104:117699.

J Med Chem. **2022** Jan 13;65(1):747-756.

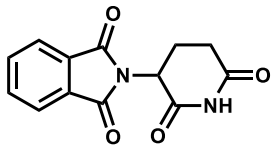


Eur J Med Chem. **2024** Apr 15;270:116328.

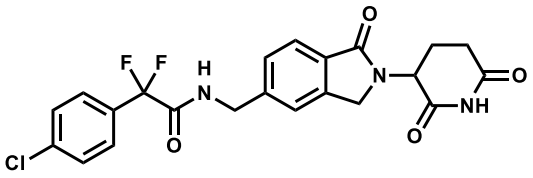
ACS Med Chem Lett. **2024** Dec 12;16(1):89-95.

J Med Chem. **2023** Dec 14;66(23):16388-16409.

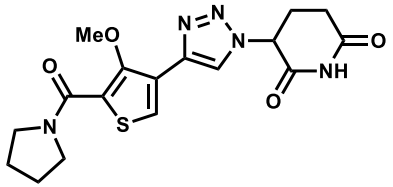
Reported CRBN Molecular Glue Degraders and Their Primary Targets



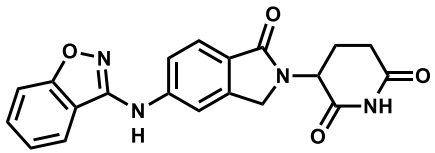
Thalidomide



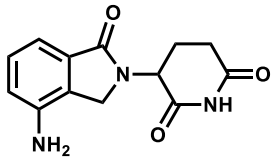
CC-90009
GSPT1



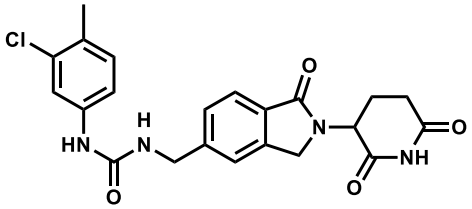
TMX-4116
CK1α



SJ3149
CK1α



Lenalidomide



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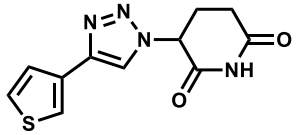
GSPT1



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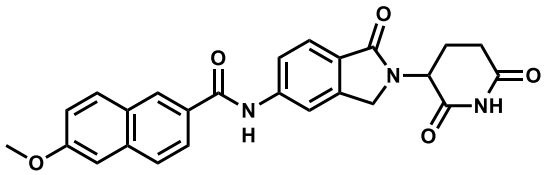
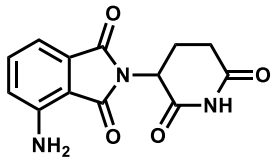
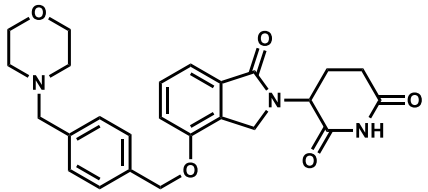


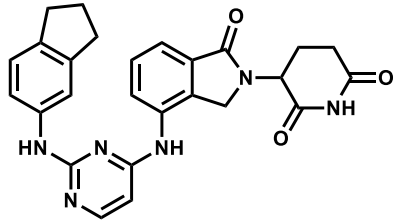
Deg35
CK1α,IKZF2



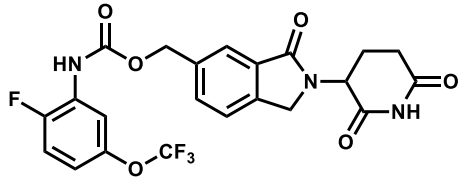
Pomalidomide



CC-220
ZFP91,IKZF1/3



ZXH-1-161
GSPT1



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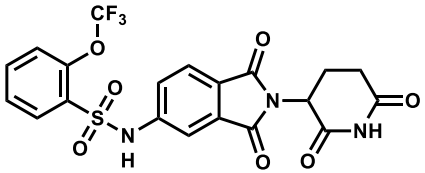

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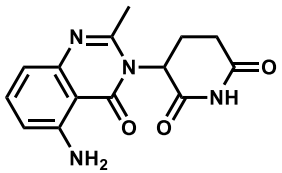
GSPT1/2



CC-122
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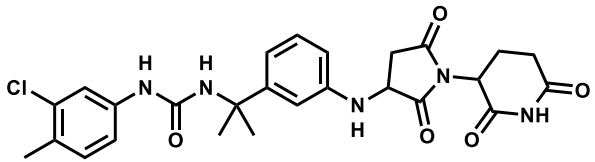
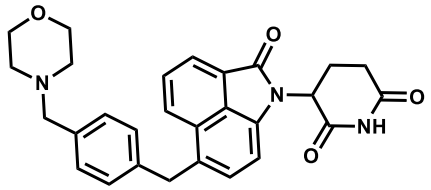


ALV2
IKZF2



CFT7544
IKZF1/3

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Nathanael S. Gray
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Article

Discovery of CRBN-Dependent WEE1 Molecular Glue Degraders from a Multicomponent Combinatorial Library

Hlib Razumkov,[#] Zixuan Jiang,[#] Kheewoong Baek,[#] Inchul You, Qixiang Geng, Katherine A. Donovan, Michelle T. Tang, Rebecca J. Metivier, Nada Mageed, Pooreum Seo, Zhengnian Li, Woong Sub Byun, Stephen M. Hinshaw, Roman C. Sarott, Eric S. Fischer,* and Nathanael S. Gray*

Cite This: *J. Am. Chem. Soc.* 2024, 146, 31433–31443
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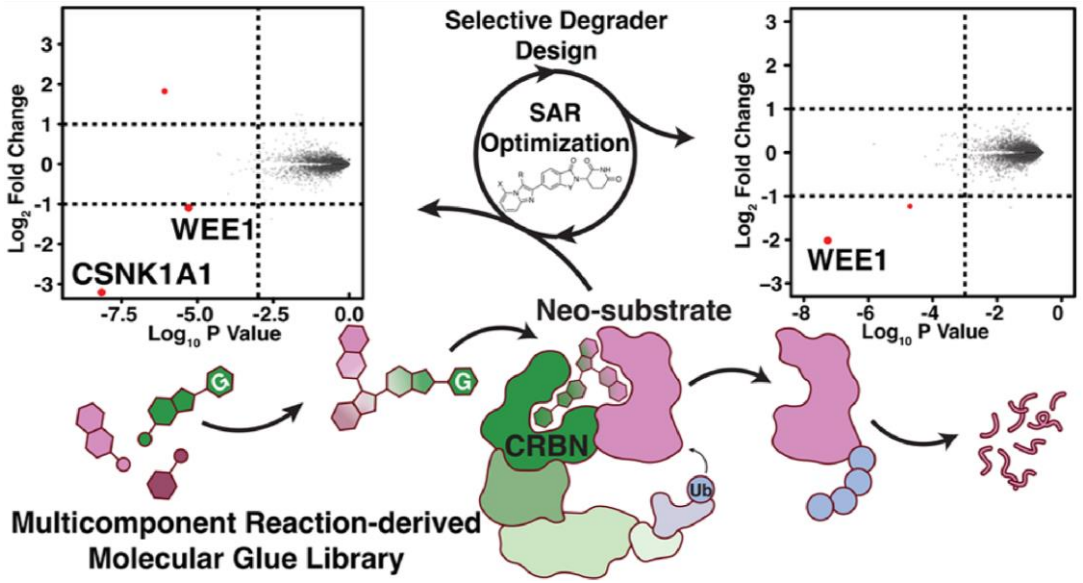


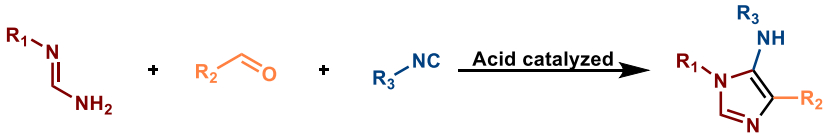
ChemPubSoc Europe
DOI: 10.1002/ejoc.201901124
EurJOC European Journal of Organic Chemistry
Minireview

Multicomponent Reactions

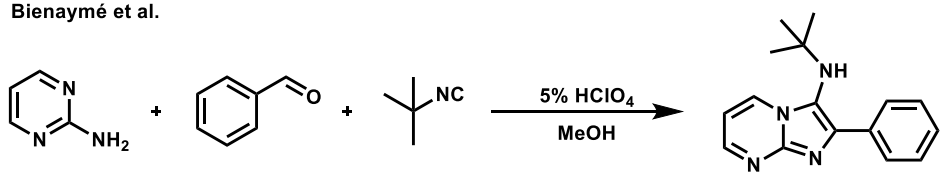
The Groebke-Blackburn-Bienaymé Reaction

André Boltjes[a] and Alexander Dömling*[a]

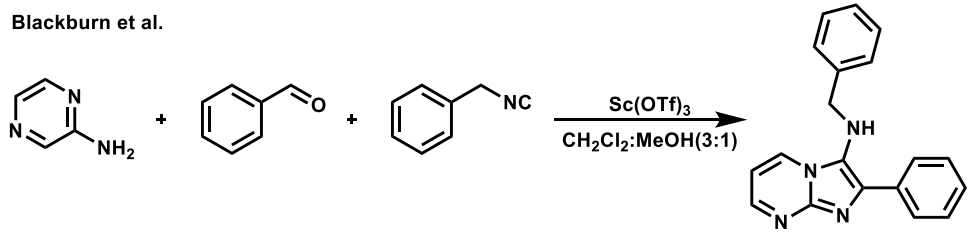
General GBB reaction:



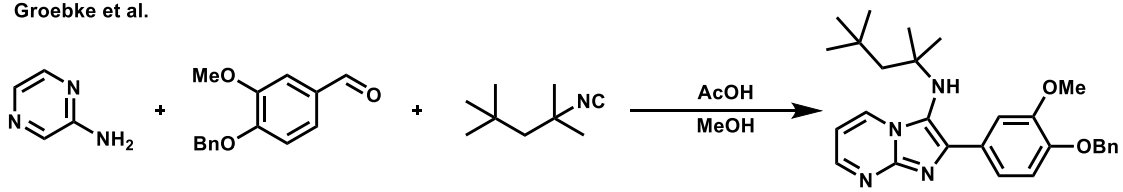
Bienaymé et al.



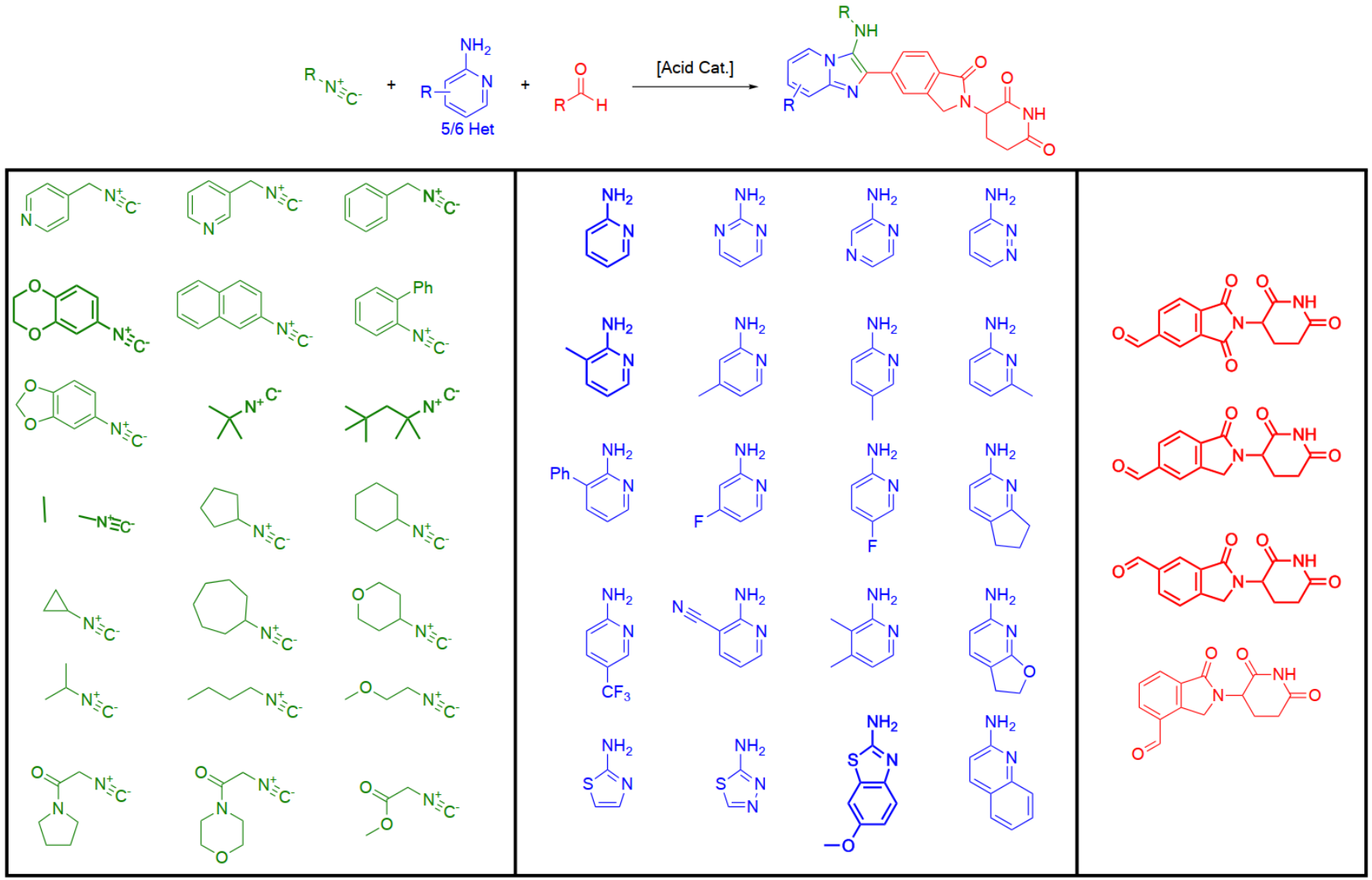
Blackburn et al.



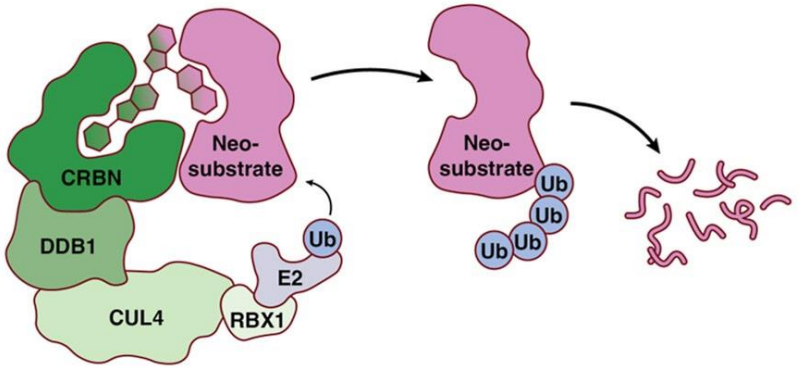
Groebke et al.

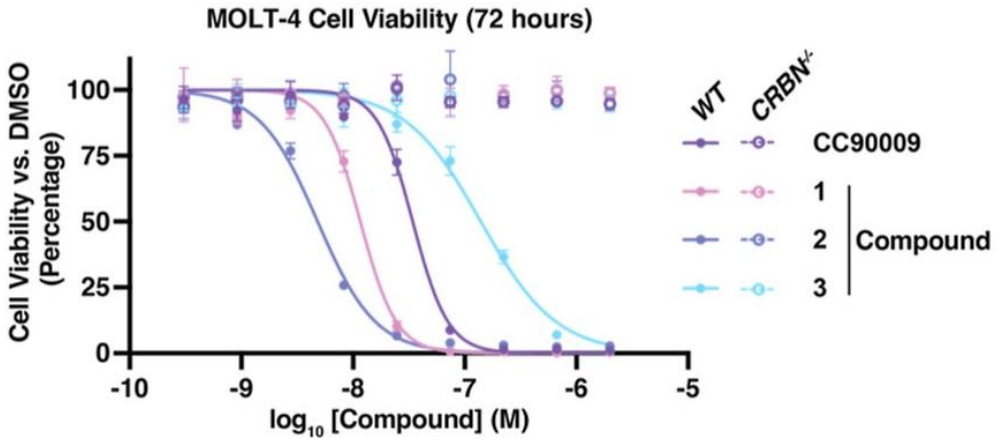


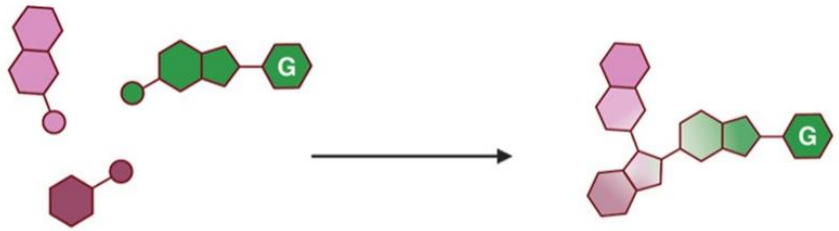
Multicomponent Reaction Synthesis of a Diverse CRBN Molecular Glue Library

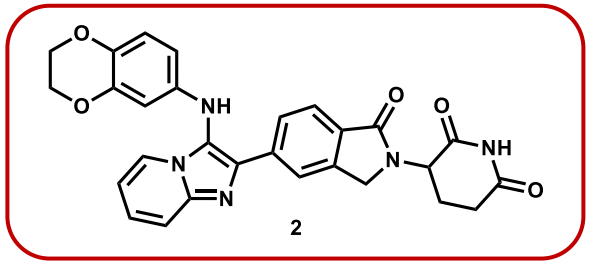


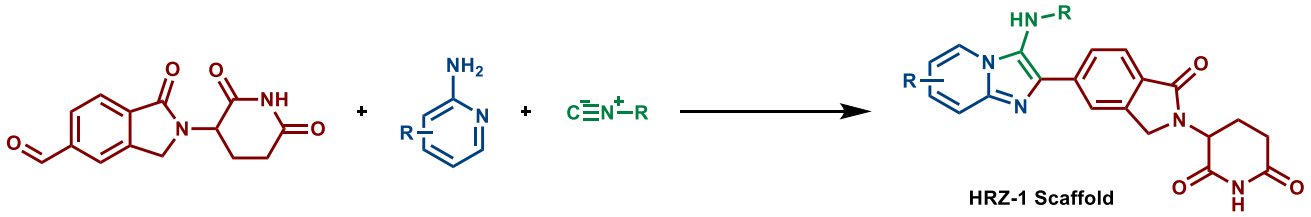
Identification of Potent WEE1/CK1α Dual Degraders

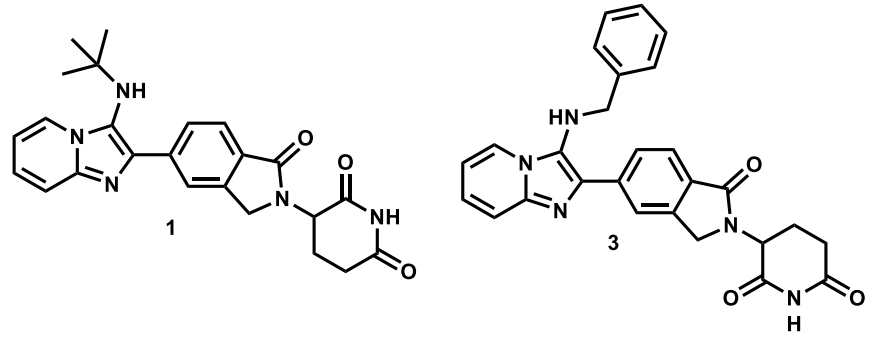




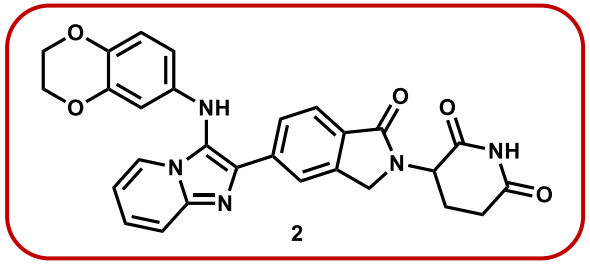


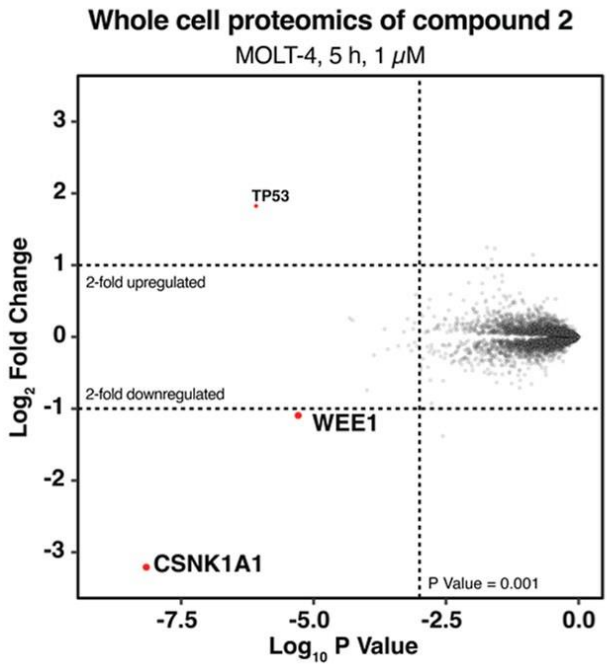


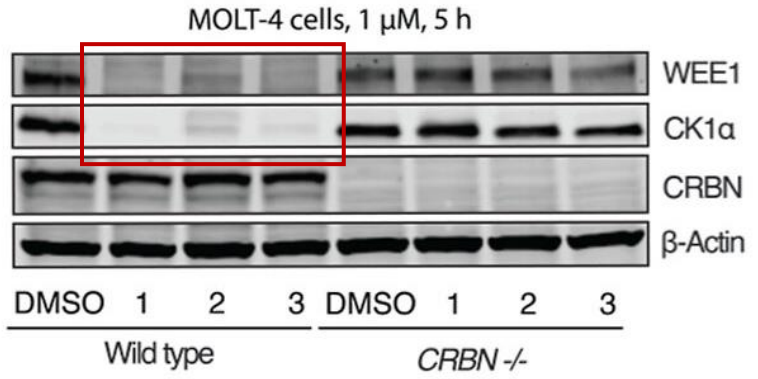


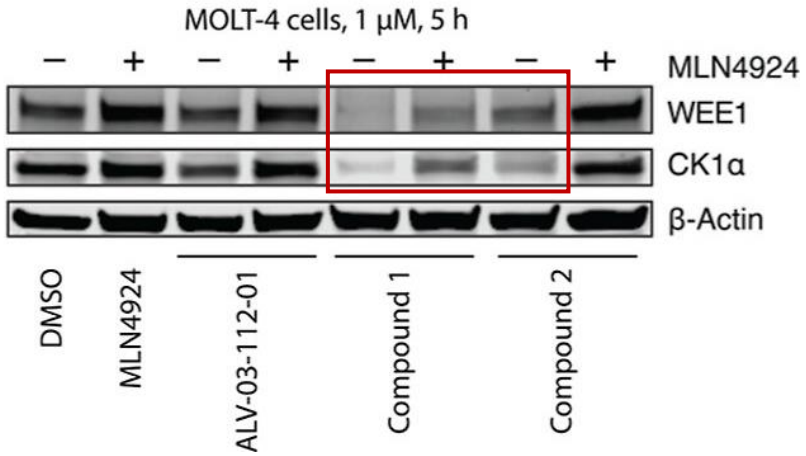


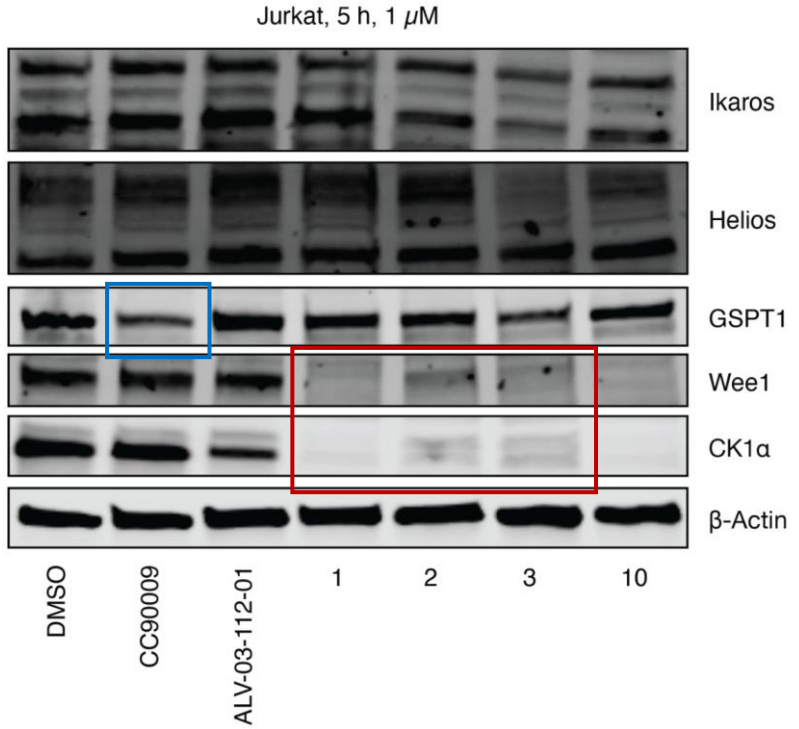
Identification of Potent WEE1/CK1α Dual Degraders



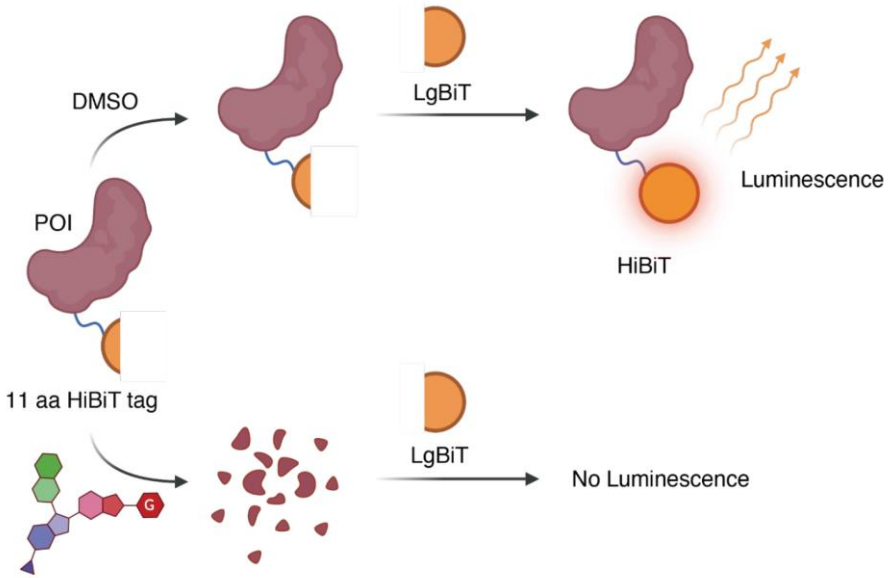


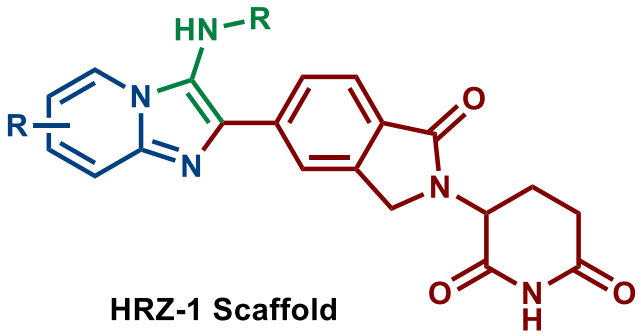




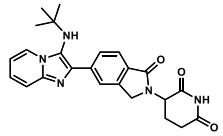
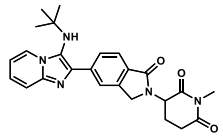
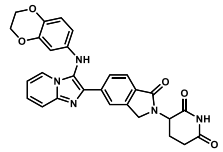
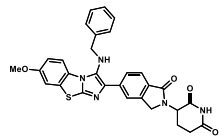
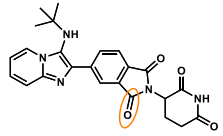
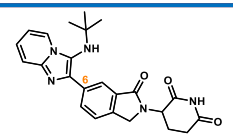
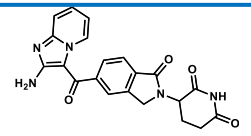


Structure−Activity Relationship of WEE1/CK1α Molecular Glue Degraders

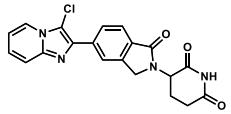
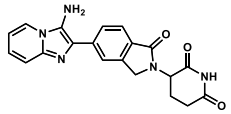
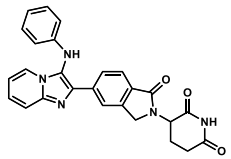
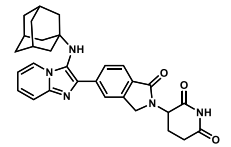
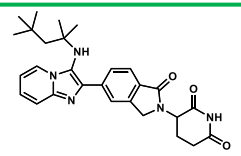
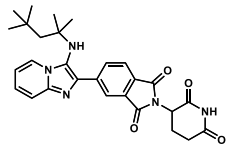
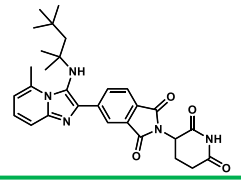


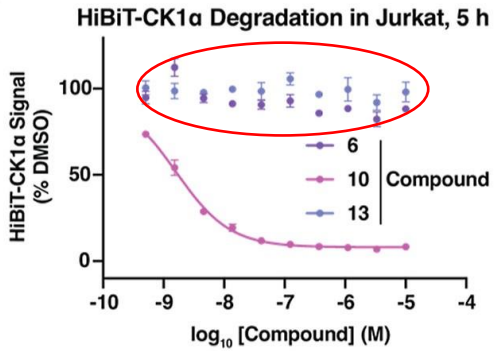


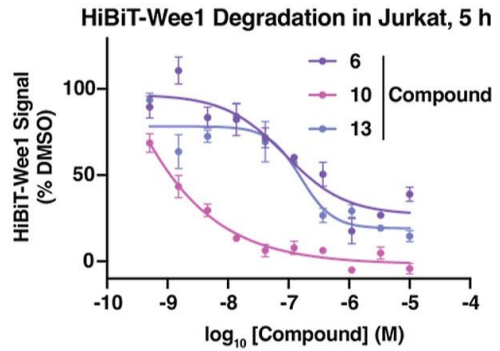
HRZ-1 Scaffold

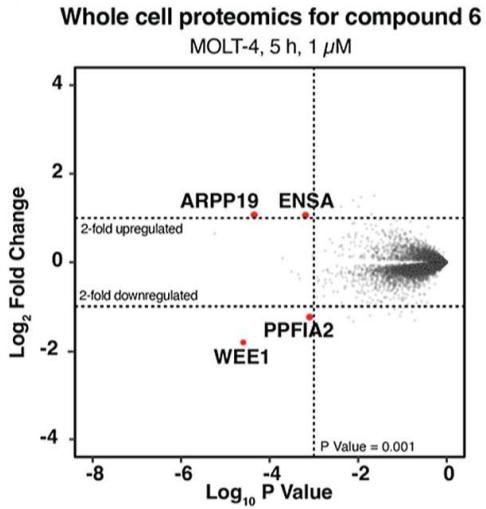
Compound	R	CK1α DC50,nM	CK1α Dmax,%	WEE1 DC50,nM	WEE1 Dmax,%
1		1.1±0.7	94	3.1±1.4	>98
1-Me		>10000	36	>10000	45
2		4.0±0.3	81	28±14	63
3		46±19	78	133±40	83
4		12±1	88	8.6±2.5	>98
5		>10000	<5	>10000	<5
6		>10000	12	91±30	61

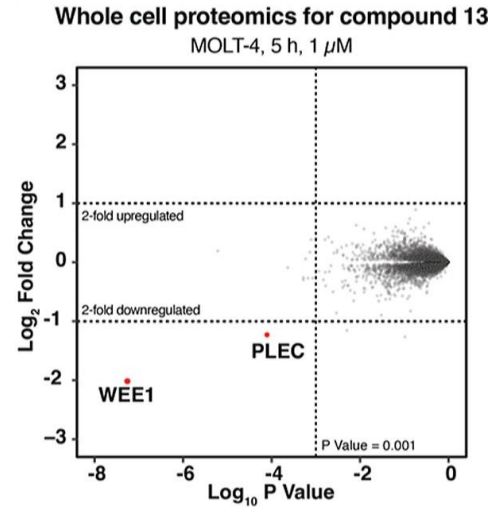
Structure−Activity Relationship of WEE1/CK1α Molecular Glue Degraders

Compound	R	CK1α DC50,nM	CK1α Dmax,%	WEE1 DC50,nM	WEE1 Dmax,%
7		10.6±0.9	84	10±8	87
8		26±3	86	18±4	97
9		1.8±0.3	83	1.9±1.1	78
10		1.6±0.5	92	1.5±0.8	>98
11		9.1±4.3	71	2.0±0.8	98
12		170±30	64	22±5	>98
13		>10000	<5	140±20	85

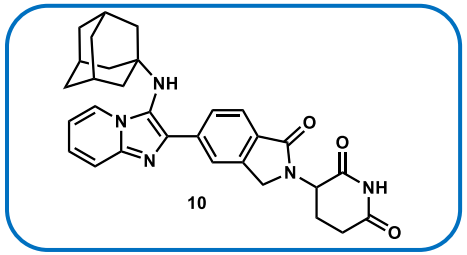


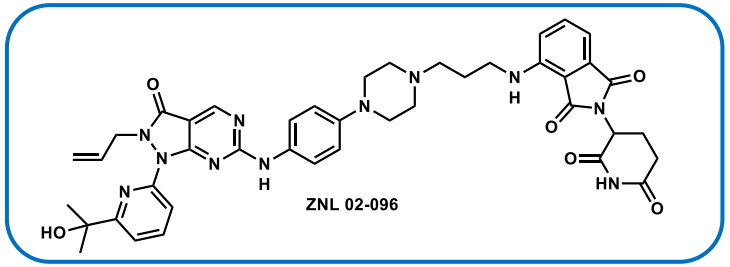


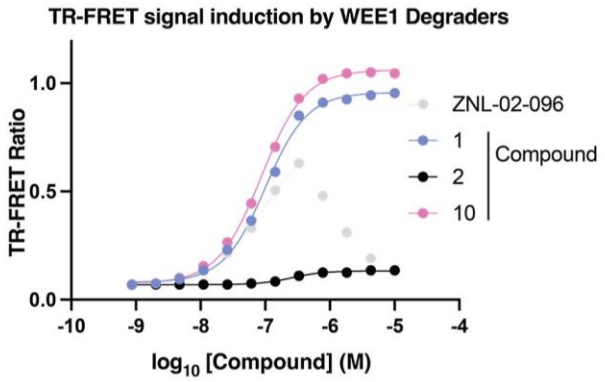


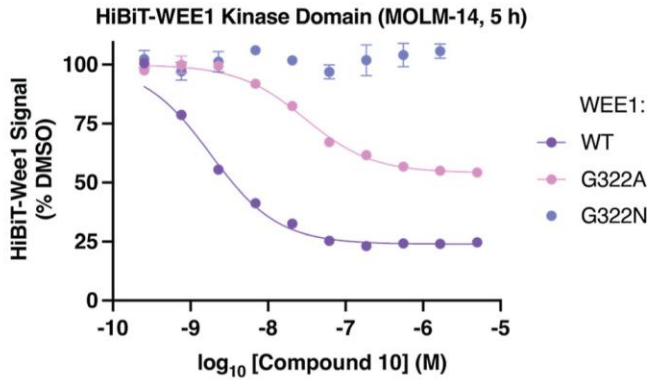


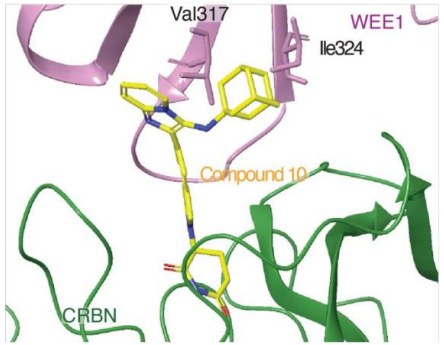
Structural analysis of Ternary Complexes

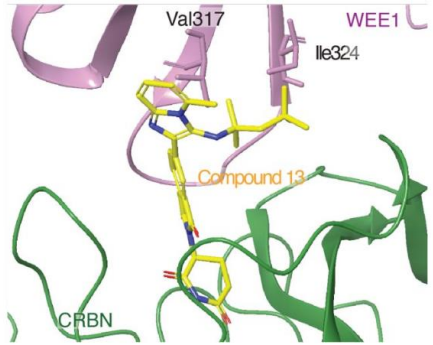


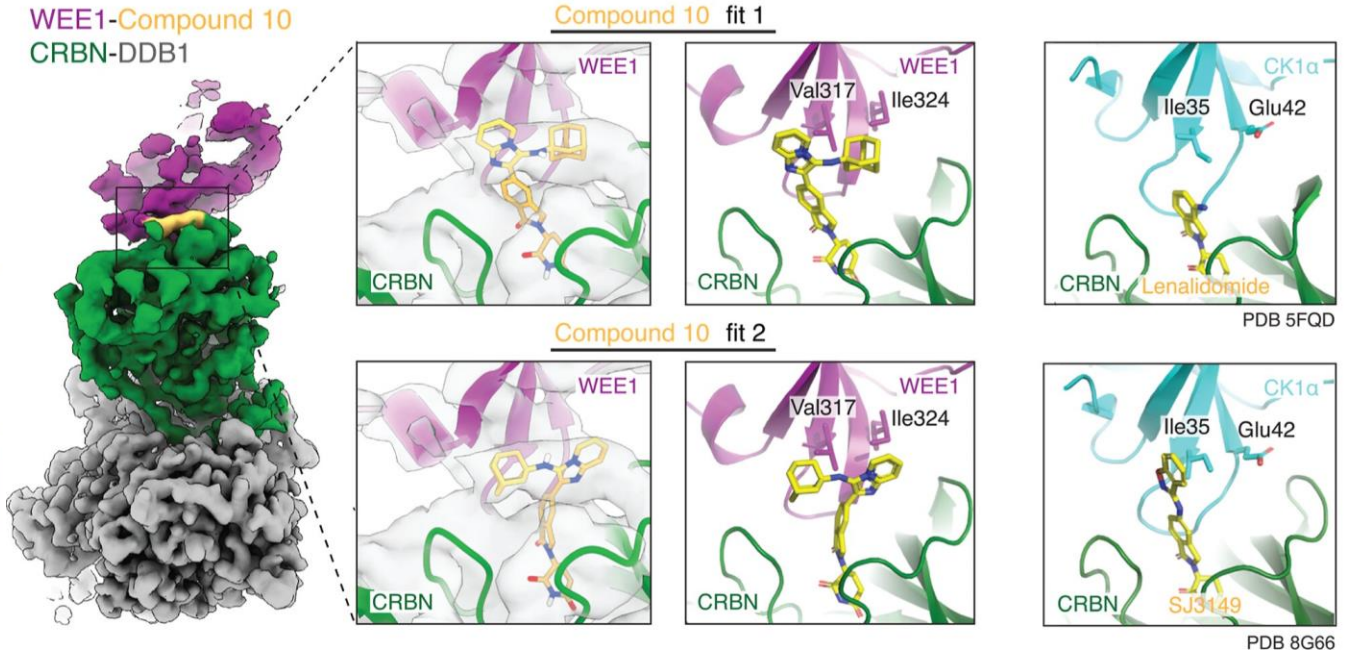




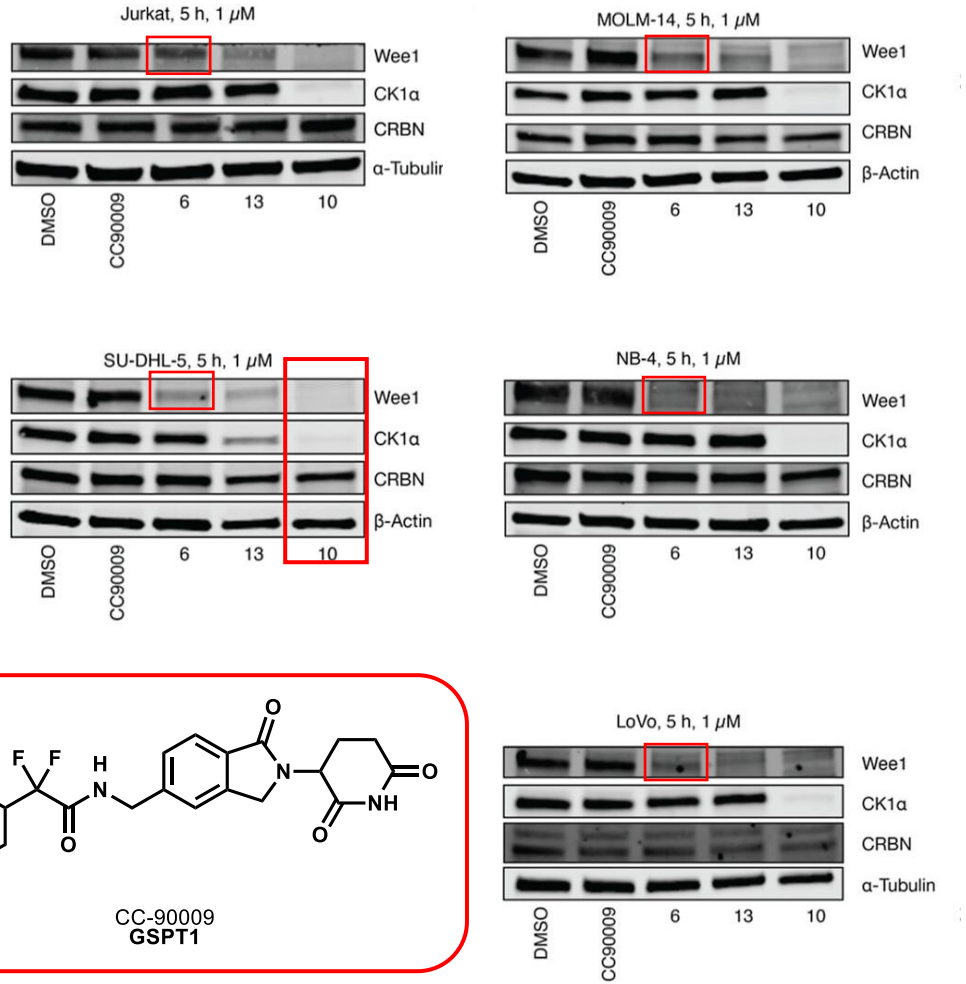


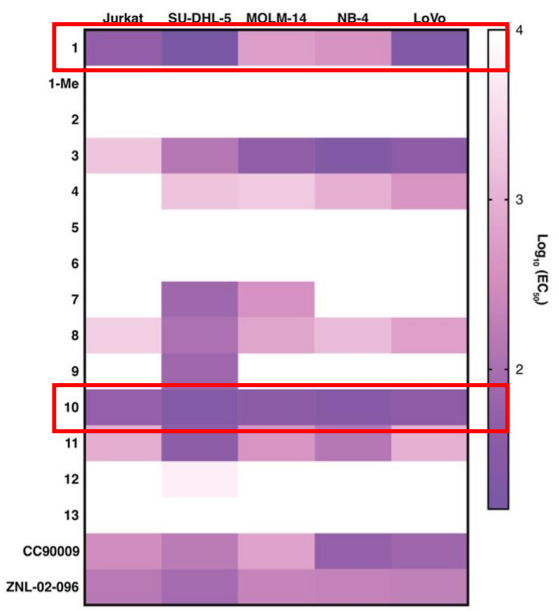


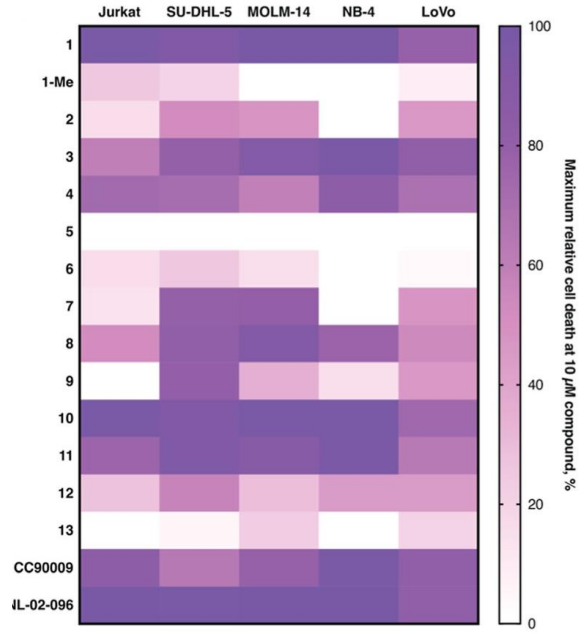




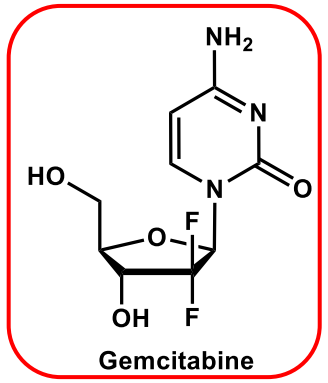
Molecular Glue Degraders Induce Target Degradation in Multiple Tumor Cell Lines



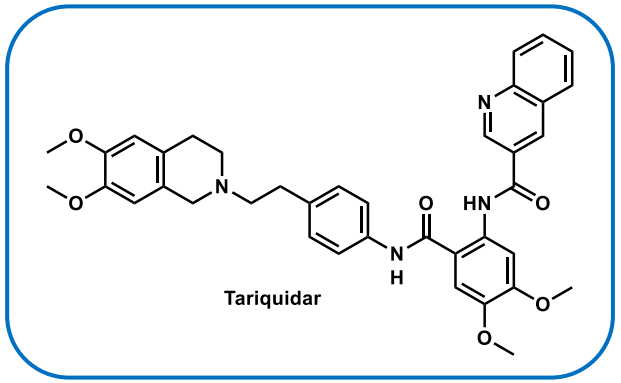




Molecular Glue Degraders Induce Target Degradation in Multiple Tumor Cell Lines



Gemcitabine



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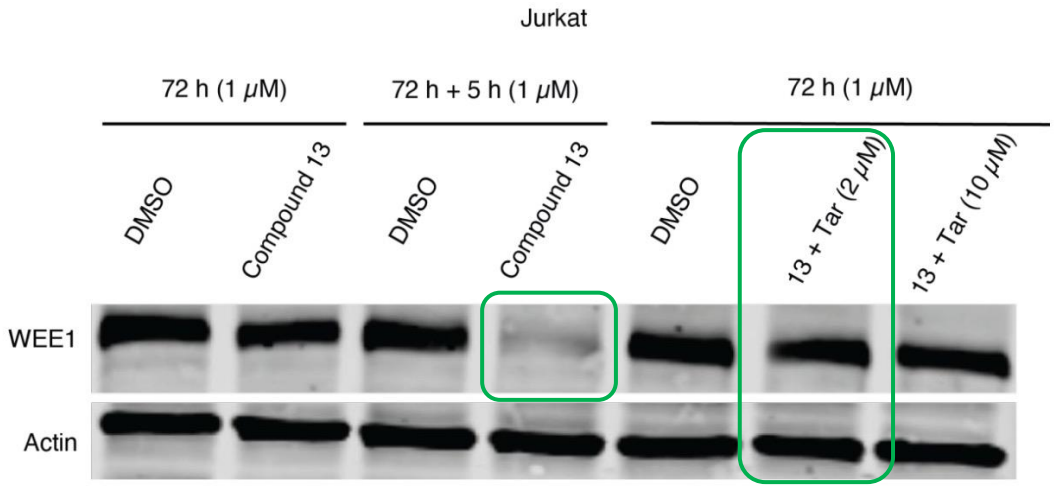

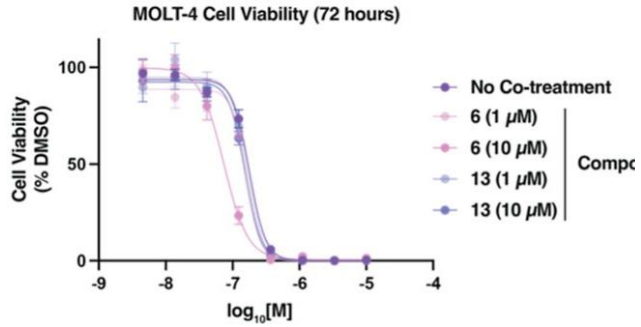

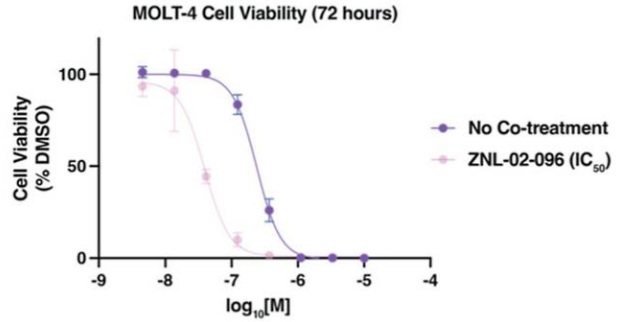

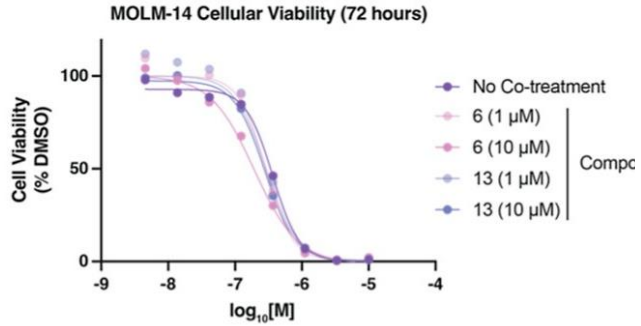

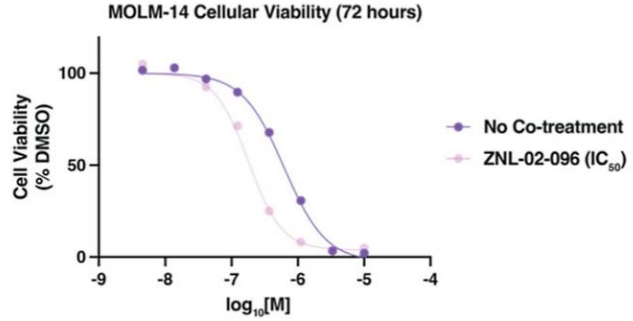

Thanks

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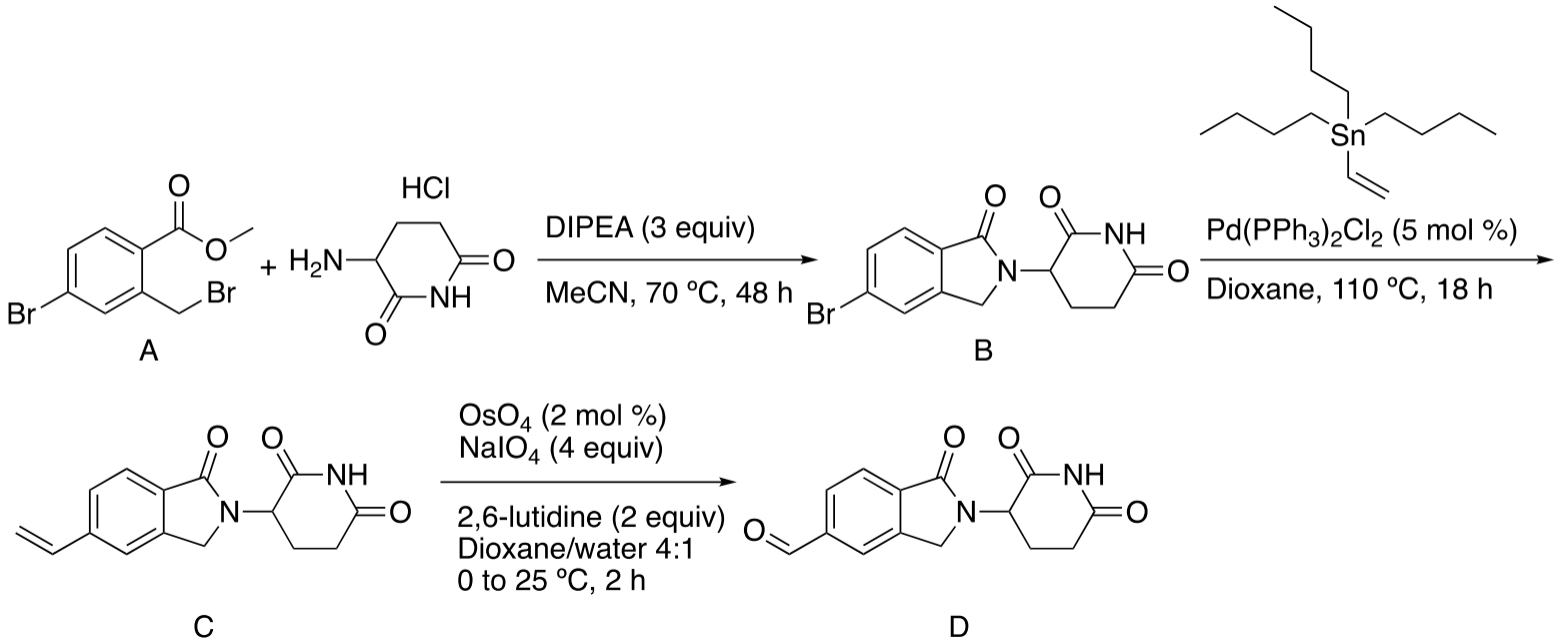

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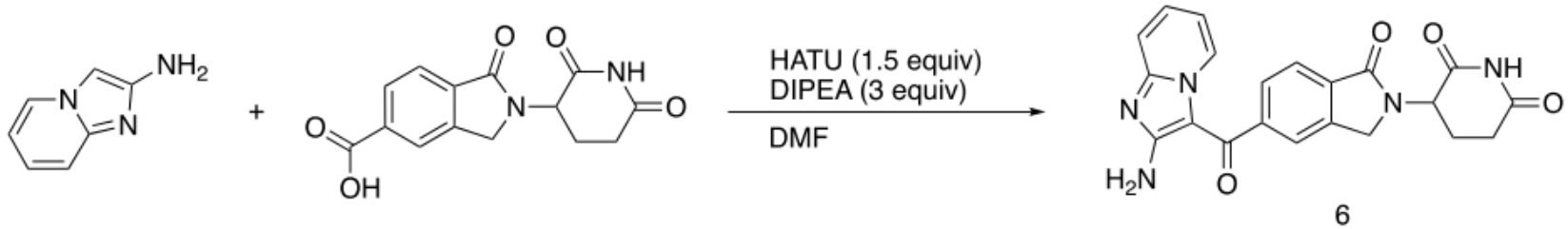
Compound 6



6

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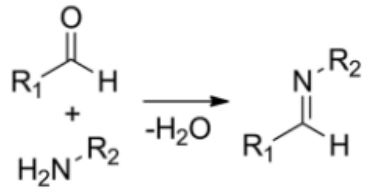

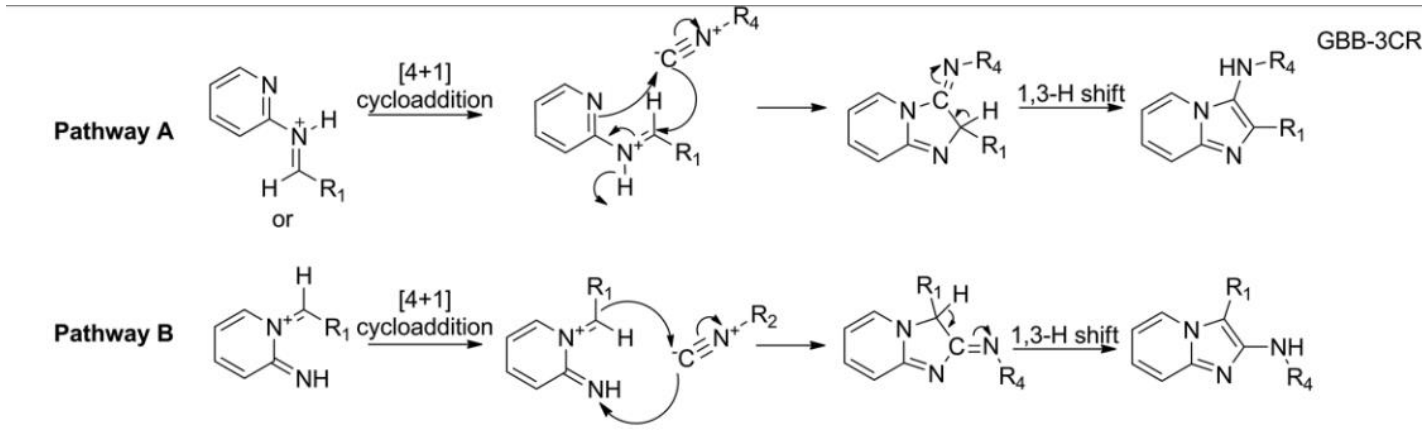

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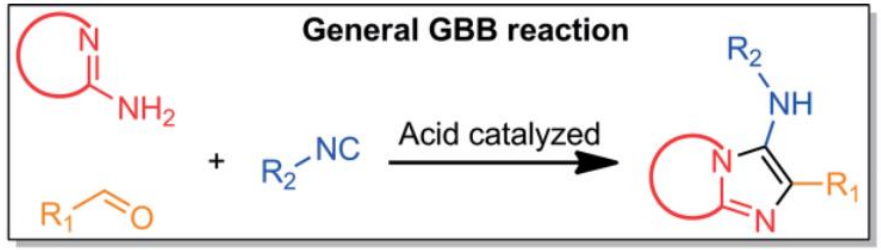
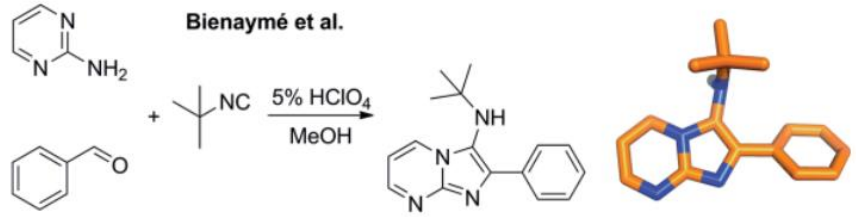


B.



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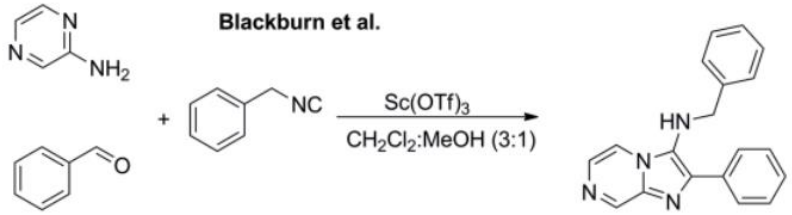
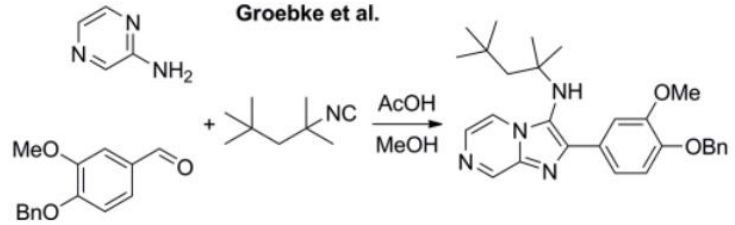


D.

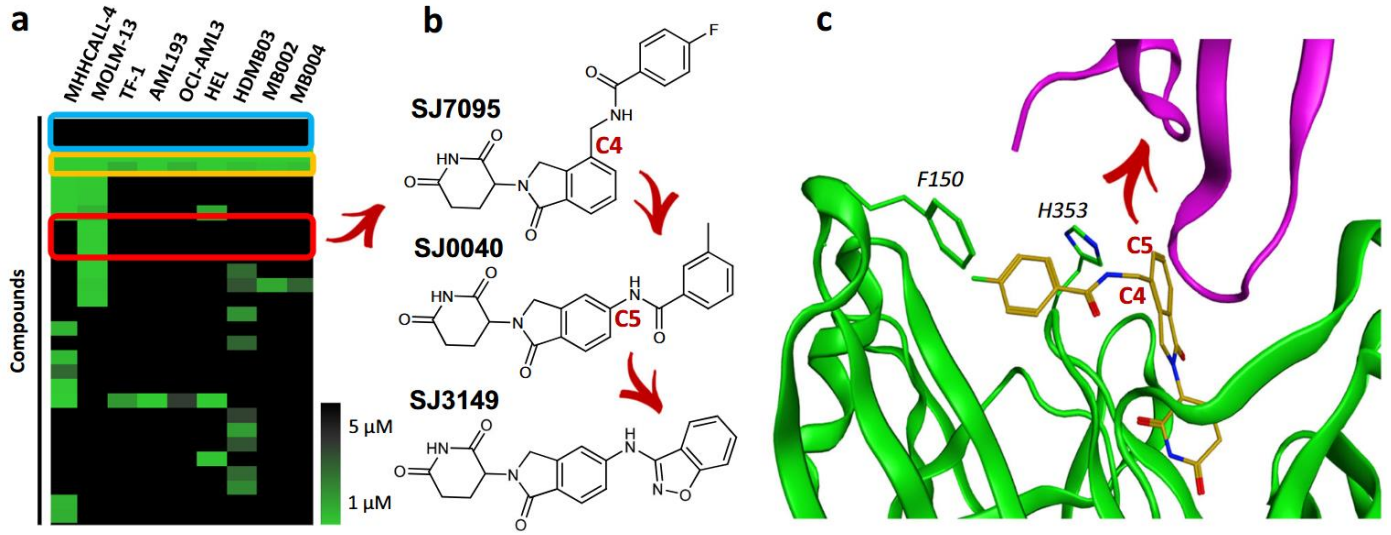


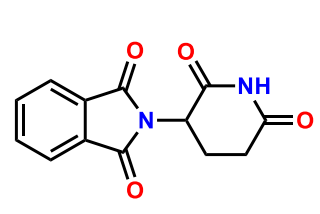
nature communications

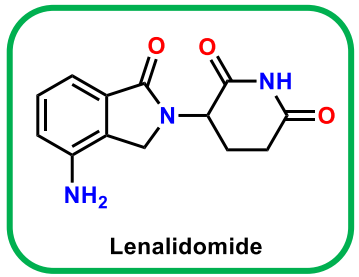
Article

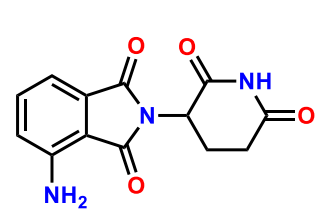
https://doi.org/10.1038/s41467-024-44698-1

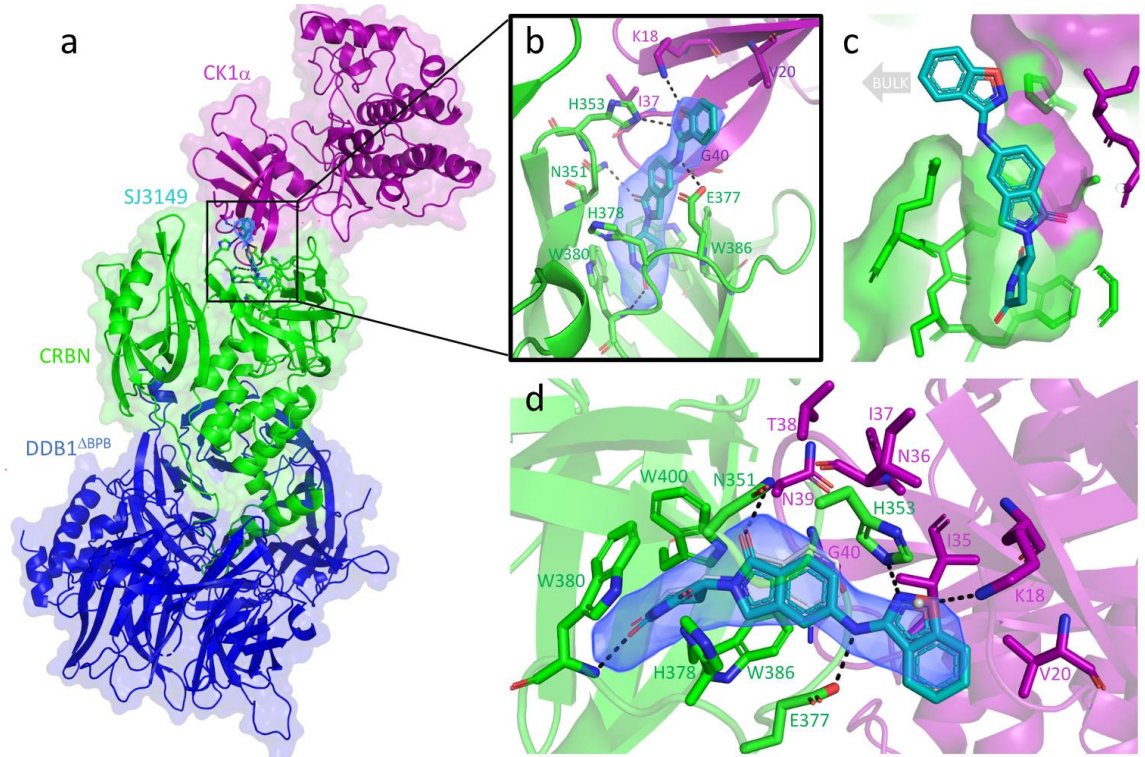
Selective CK1α degraders exert antiproliferative activity against a broad range of human cancer cell lines

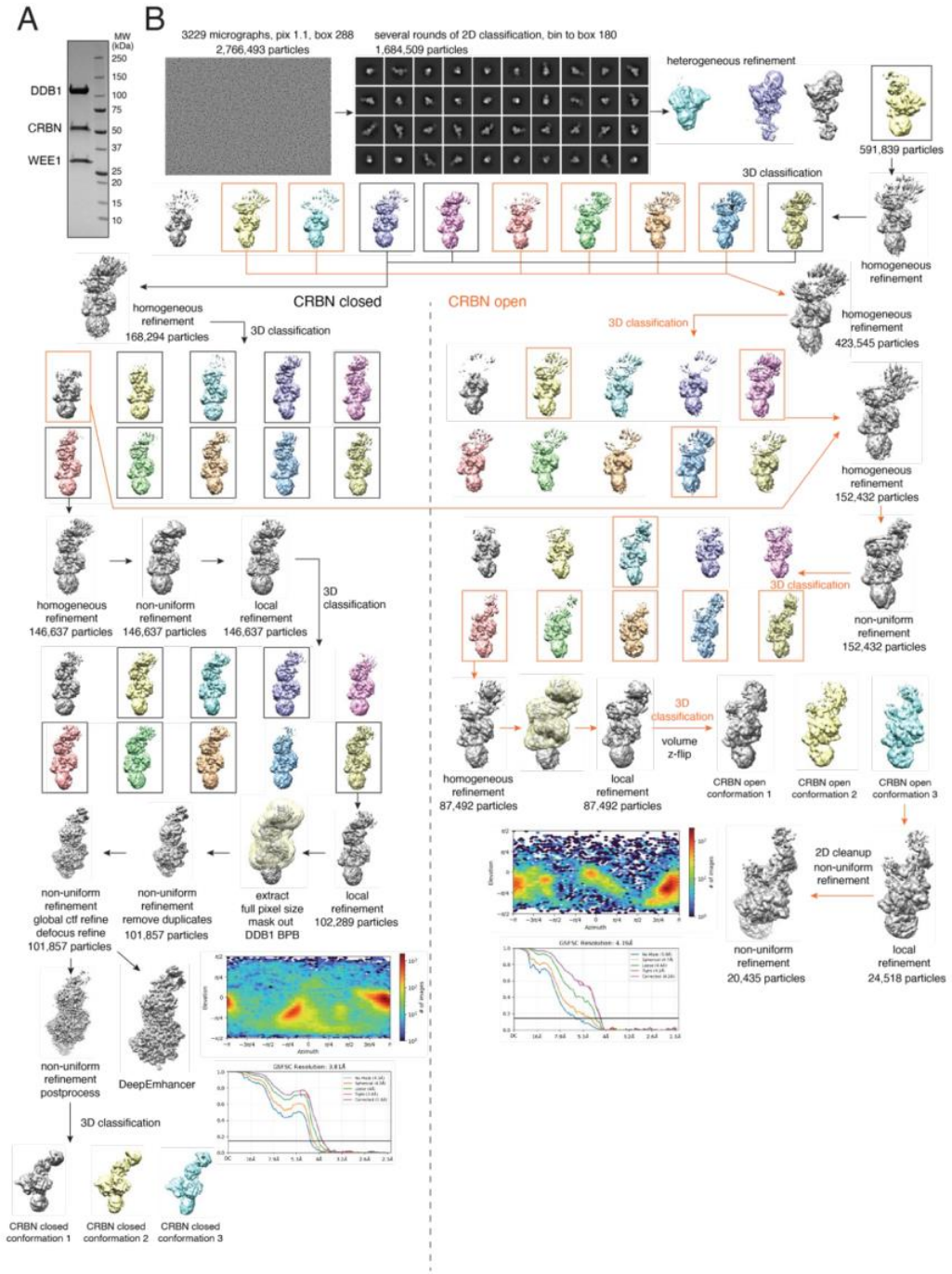


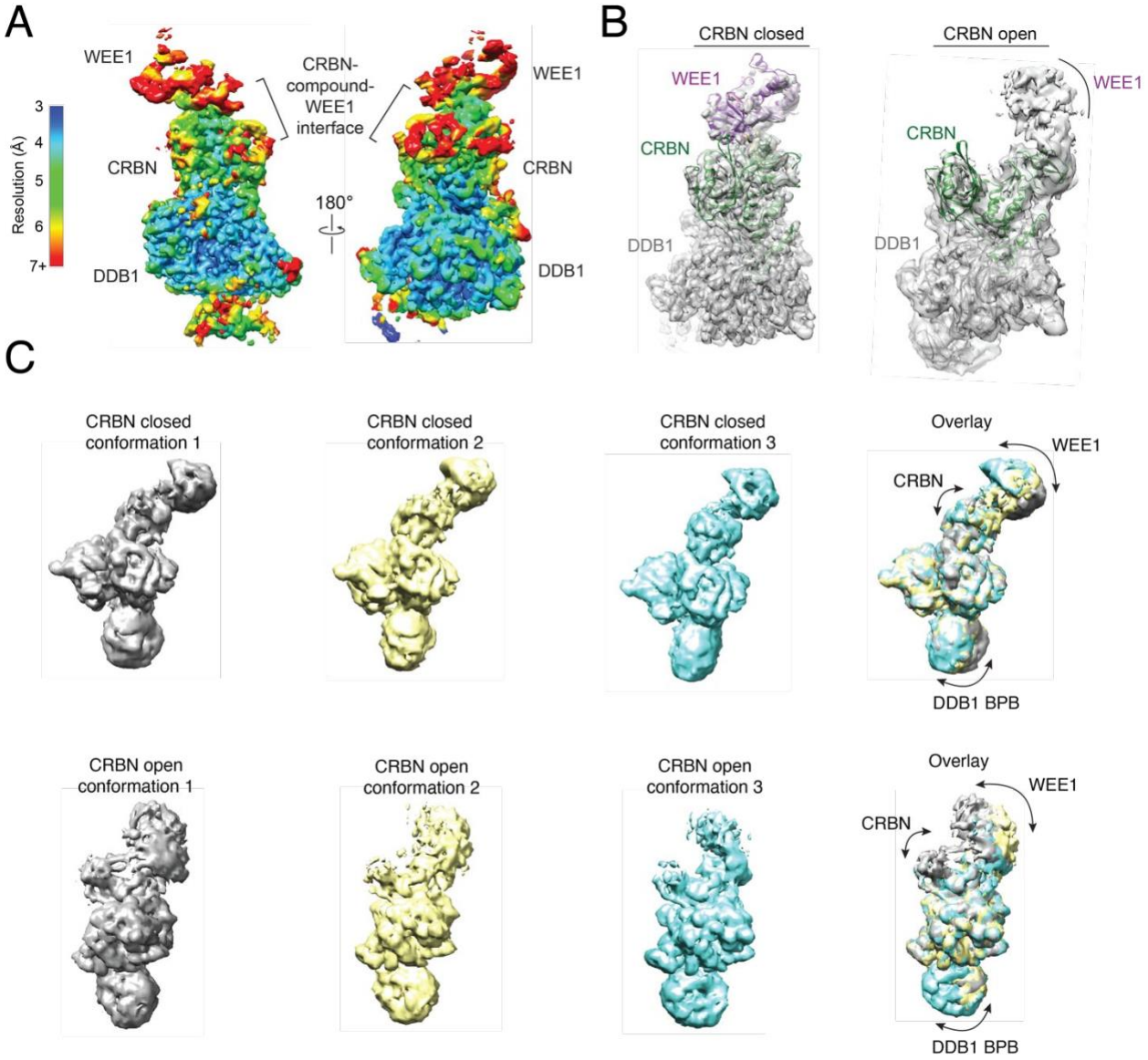


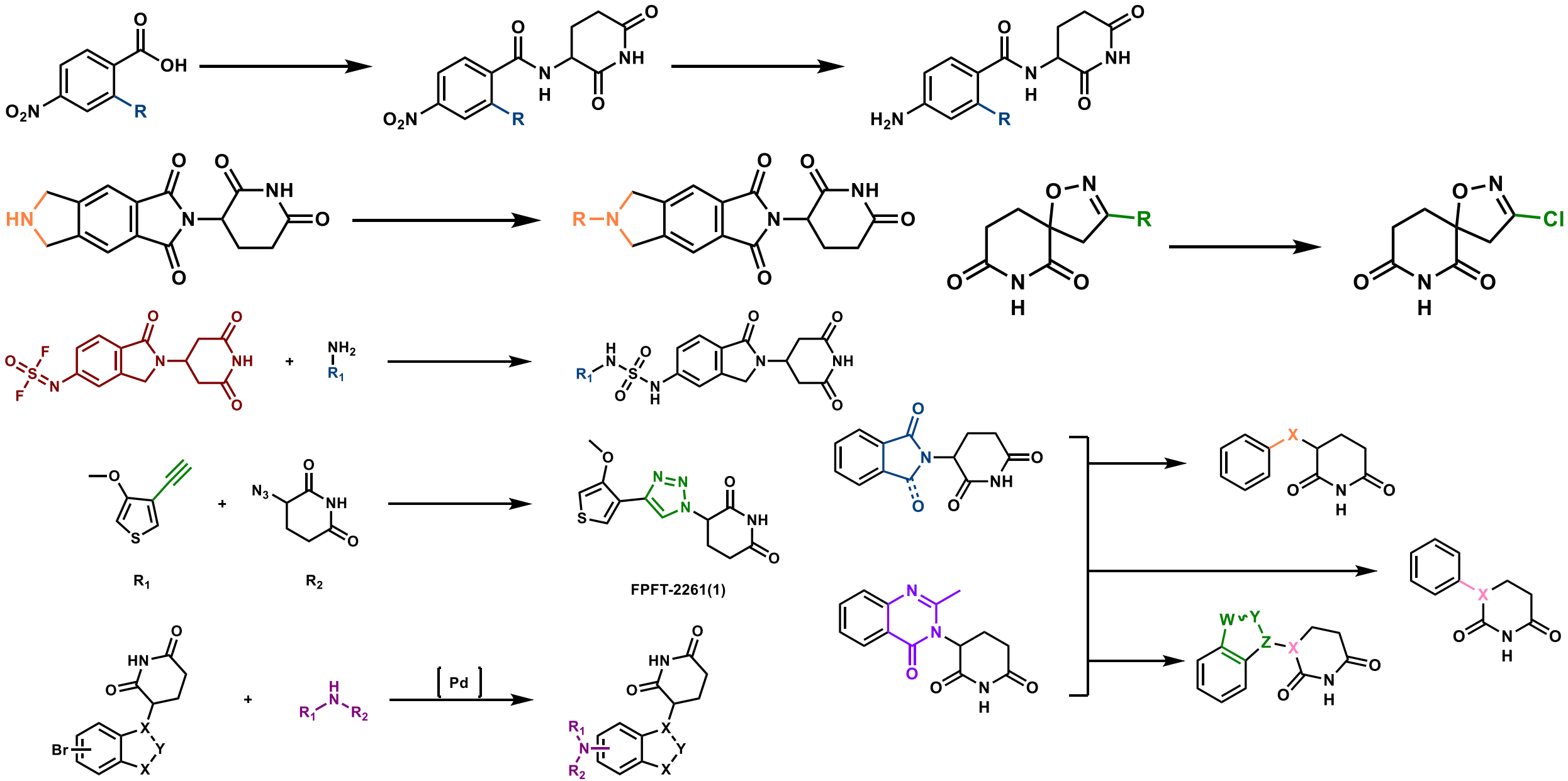







A
B
MW (kDa)
250
150
100
75
50
37
25
20
15
10
DDB1
CRBN
WEE1
3229 micrographs, pix 1.1, box 288
2,766,493 particles
several rounds of 2D classification, bin to box 180
1,684,509 particles
heterogeneous refinement
591,839 particles
3D classification
homogeneous refinement
homogeneous refinement
423,545 particles
CRBN closed
CRBN open
3D classification
homogeneous refinement
168,294 particles
3D classification
homogeneous refinement
146,637 particles
non-uniform refinement
146,637 particles
local refinement
146,637 particles
3D classification
homogeneous refinement
152,432 particles
non-uniform refinement
152,432 particles
3D classification
homogeneous refinement
87,492 particles
local refinement
87,492 particles
3D classification
volume z-flip
CRBN open conformation 1
CRBN open conformation 2
CRBN open conformation 3
2D cleanup non-uniform refinement
local refinement
24,518 particles
non-uniform refinement
20,435 particles
non-uniform refinement global ctf refine defocus refine
101,857 particles
non-uniform refinement remove duplicates
101,857 particles
extract full pixel size mask out DDB1 BPB
local refinement
102,289 particles
non-uniform refinement postprocess
DeepEmhancer
3D classification
CRBN closed conformation 1
CRBN closed conformation 2
CRBN closed conformation 3


A
Resolution (Å)
3
4
5
6
7+
WEE1
CRBN
DDB1
CRBN-compound-WEE1 interface
180°
B
CRBN closed
CRBN open
C
CRBN closed conformation 1
CRBN closed conformation 2
CRBN closed conformation 3
Overlay
DDB1 BPB
CRBN open conformation 1
CRBN open conformation 2
CRBN open conformation 3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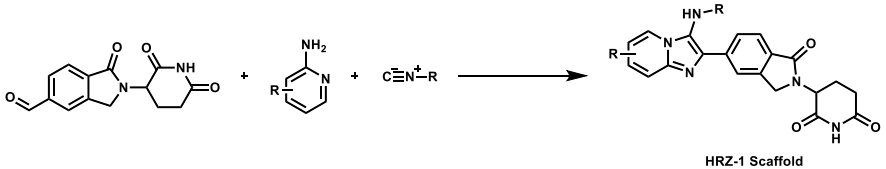
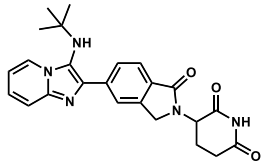


HRZ-1 Scaffold



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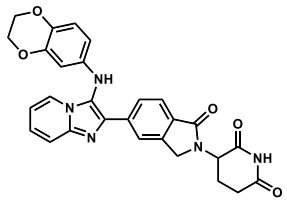

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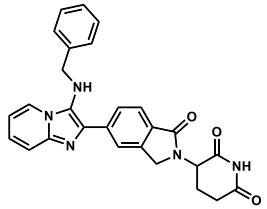

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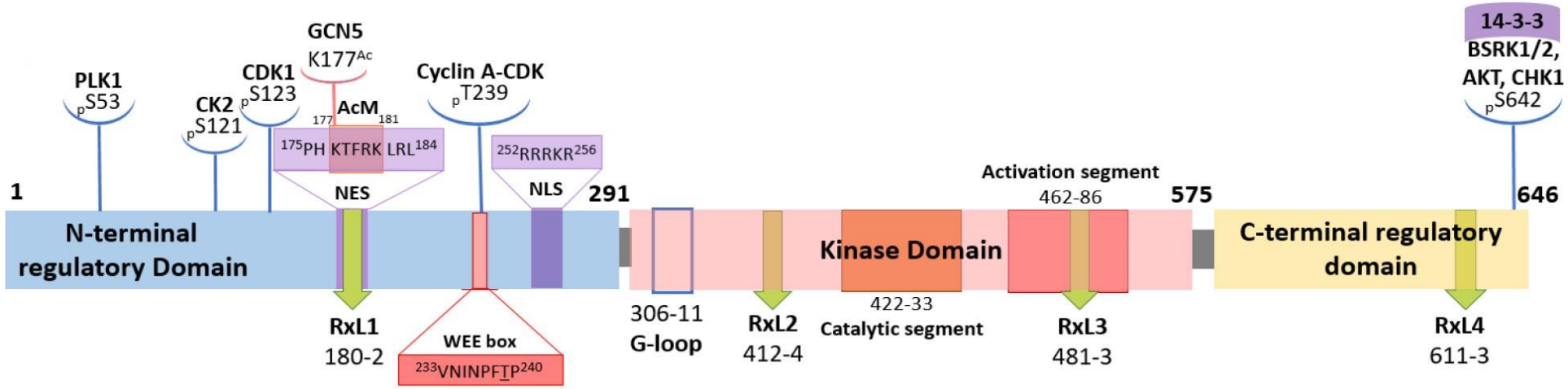

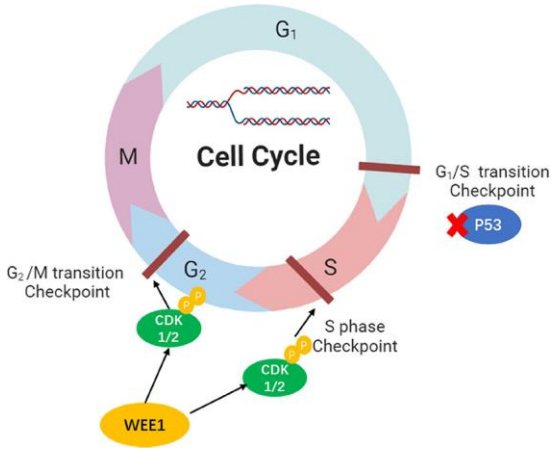

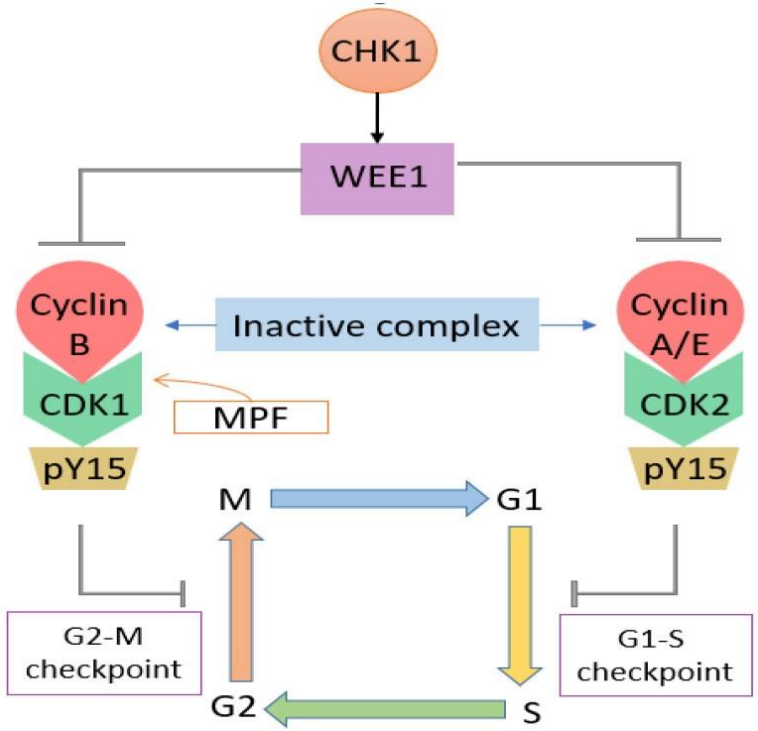

WEE1 function	Epigenic modification	Checkpoint regulation	
Regulate	Histone transcription	G1-S Checkpoint	G2-M checkpoint
WEE1 target	H2B	CDK2	CDK1
WEE1 action	Block histone transcription	S-phase delay	G2-arrest
Ensure	Appropriate Histone stoichiometry	genetic integrity	Daughter cell maturation
Result of Inactive WEE1	Mitotic catastrophe		