Protein Targeting Chimeras strategy in favour of the degradation of CK2.

A STRUCTURAL POINT OF VIEW.

SAPIENZA
UNIVERSITÀ DI ROMA

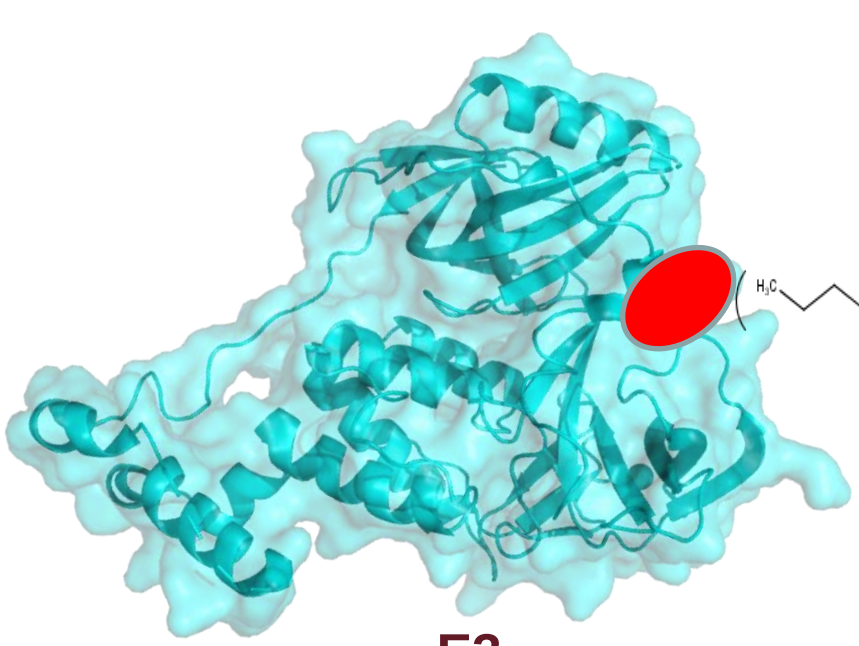
CEU | *Universidad San Pablo*

Facoltà di Farmacia e Medicina
Corso di Laurea in Biotecnologie Farmaceutiche
Tesi Sperimentale in Chimica Farmaceutica
a.a. 2018/2019

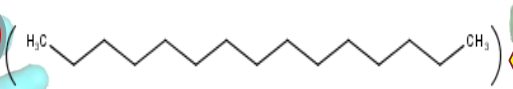
Laureando: Viscovo Marco
Matricola: 1601157

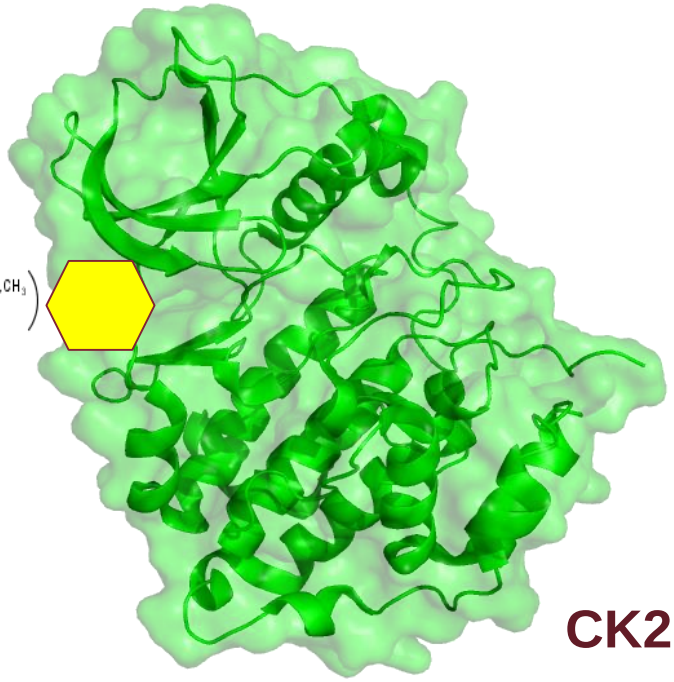
Relatore: Prof. Rino Ragno
Correlatore: Claire Coderch Boué PhD

1. Aim of the study

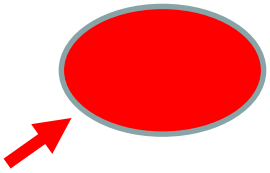


E3

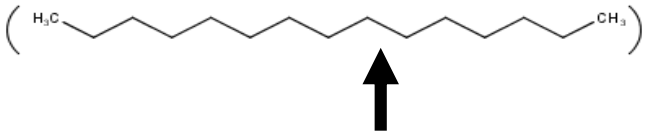




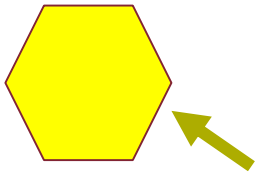
CK2



degradation machinery-recruiting portion

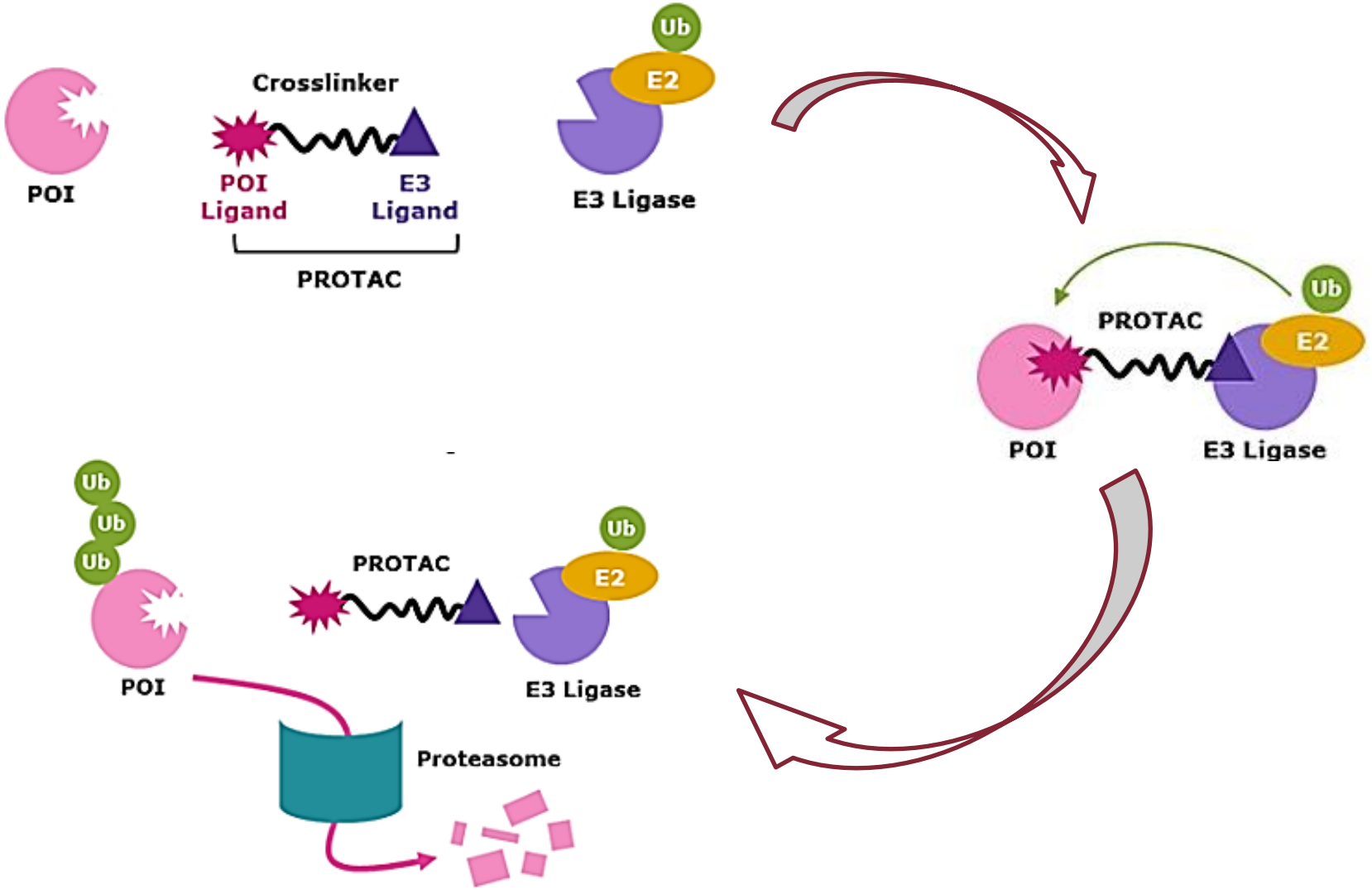


Generic linker



target protein-binding moiety

2. Introduction: PROTAC



3. Workflow

1.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156767 Biological Macromolecular Structures Enabling Breakthroughs in Research and Education
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Visualize
Analyze
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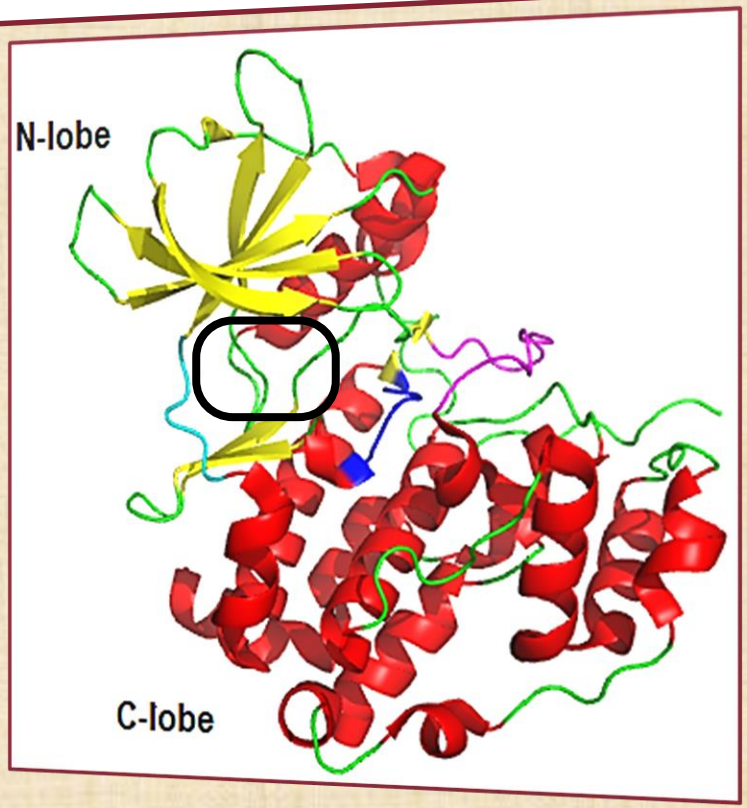
Search Options
Drill Down by Categories
Advanced Search
Explore the PDB Archive
Organism
Homo sapiens (45582)
Escherichia coli (9783)
Mus musculus (6663)
Saccharomyces cerevisiae (4401)
synthetic construct (4246)
Rattus norvegicus (3121)
Bos taurus (2951)
Other (81381)

About CK2

- Casein Kinase 2 (CK2) is a constitutively active non-specific serine/threonine kinase
- key regulator of many cellular processes, such as cellular proliferation, anti-apoptotic mechanisms and proangiogenic signalling
- Elevated CK2 expression and activity are related to blood tumours and solid tumours

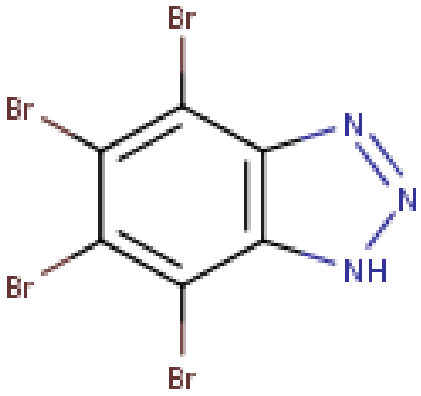


PDB code: 3NGA

2. Introduction: CK2

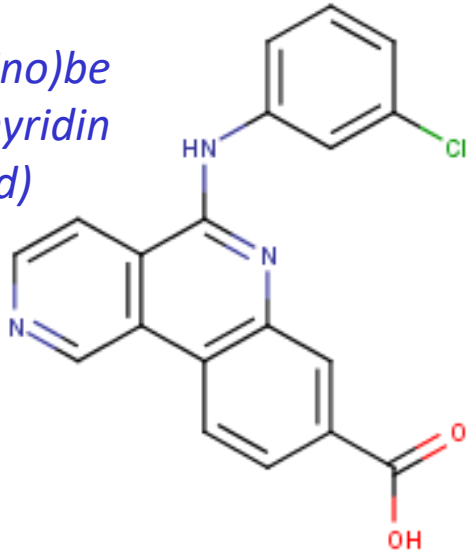
TBB *(4,5,6,7-tetrabromobenzotriazole)*

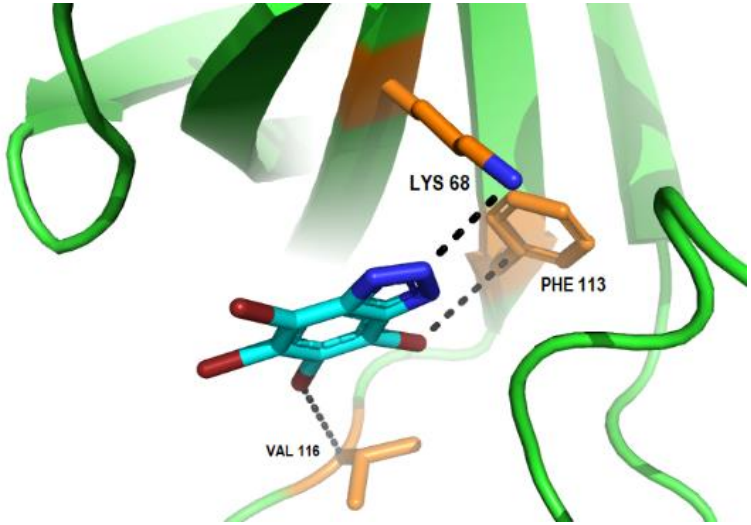
IC_{50} = 0.35 µM

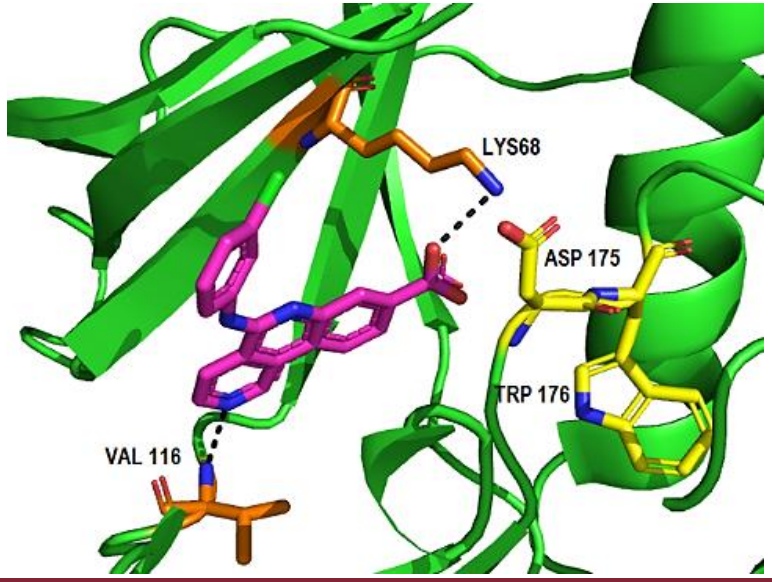


CX-4945 *(5-((3-Chlorophenyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid)*

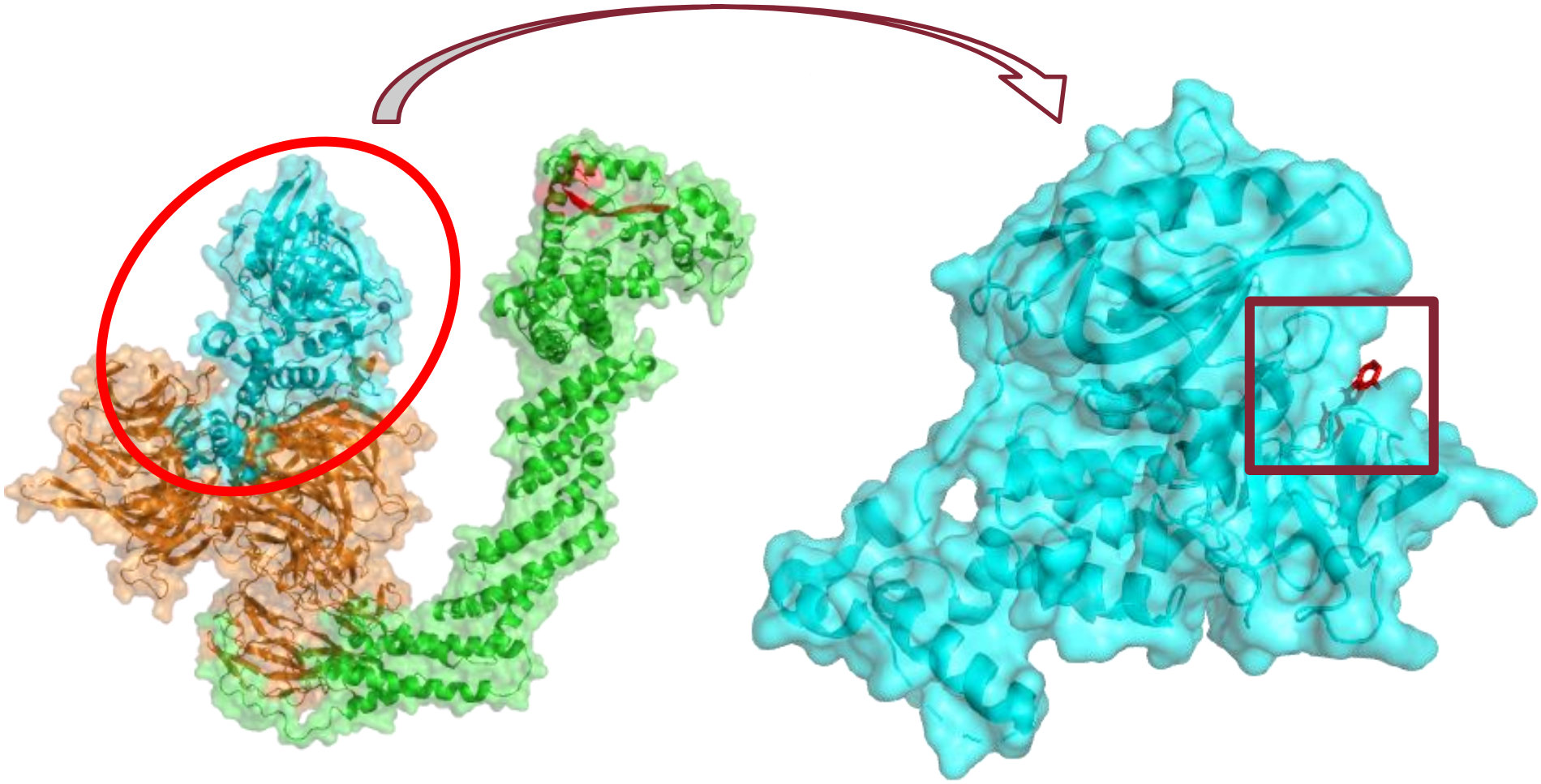
IC_{50} = 0.03 µM





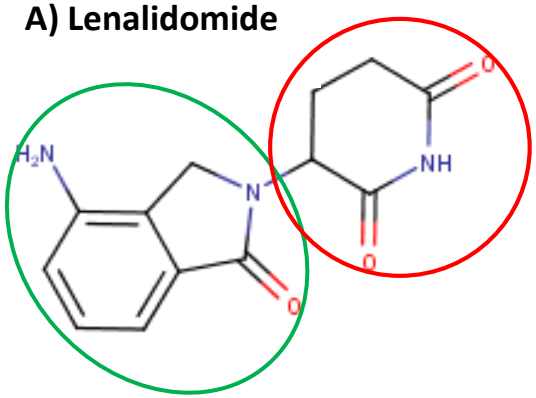


2. Introduction: E3-LIGASE CRL4^{CRBN}



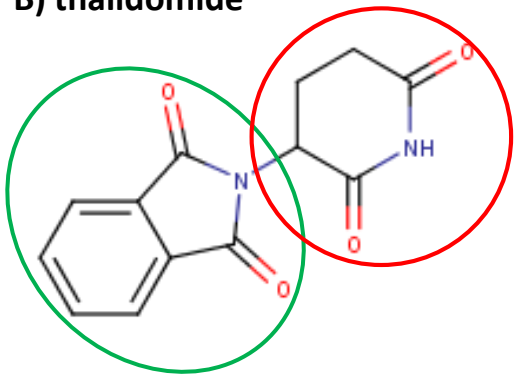
2. Introduction: E3-LIGASE CRL4^{CRBN}

A) Lenalidomide



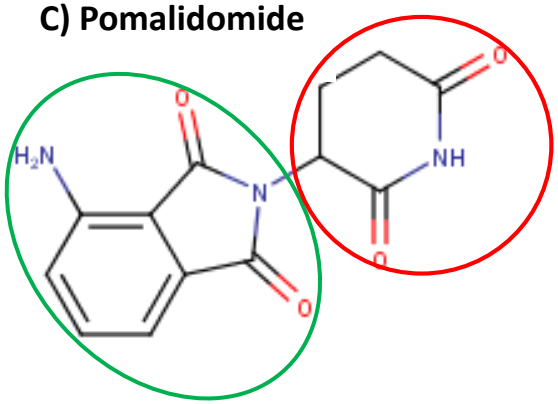
IC_{50} da aggiungere

B) thalidomide

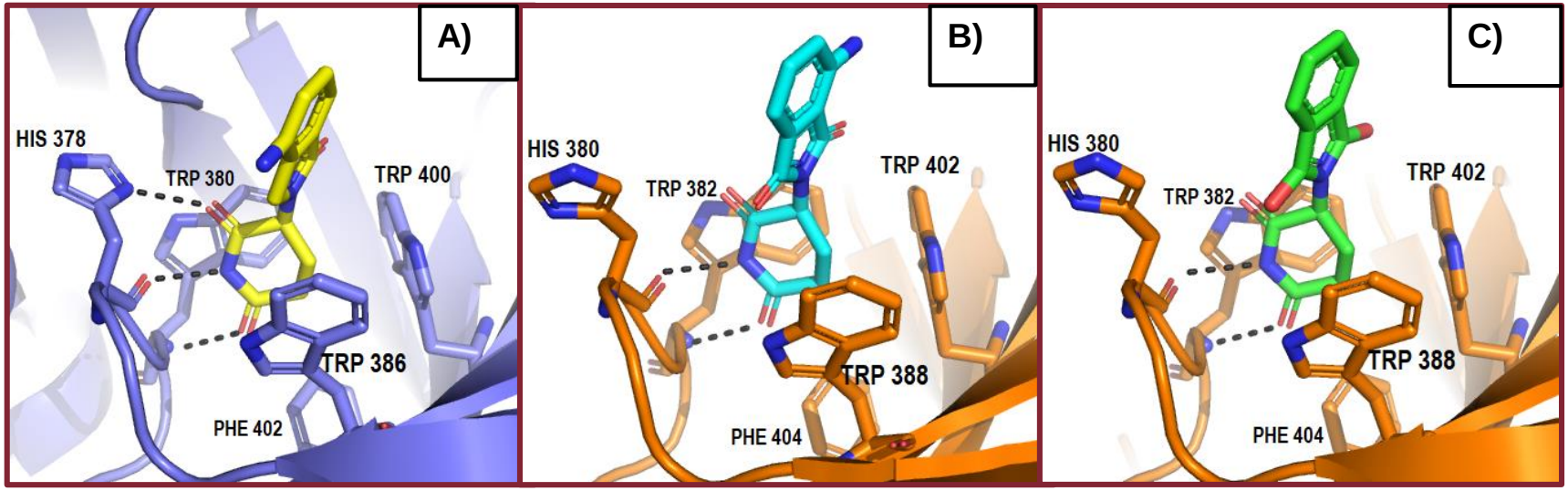


IC_{50} = da aggiungere

C) Pomalidomide



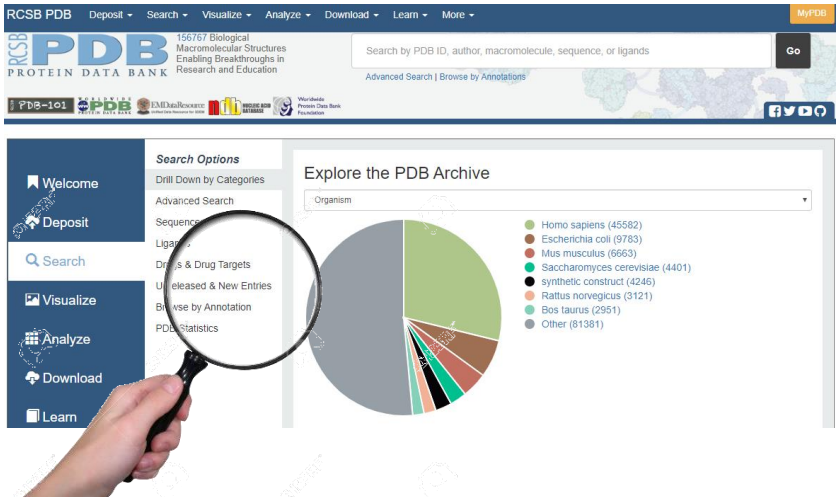
IC_{50} = da aggiungere



Petzold, G., Fischer, E. S. & Thomä, N. H. Structural basis of lenalidomide-induced CK1α degradation by the CRL4CRBN ubiquitin ligase. *Nature* 532, 127–130 (2016). *Struct*

3. Workflow

1.



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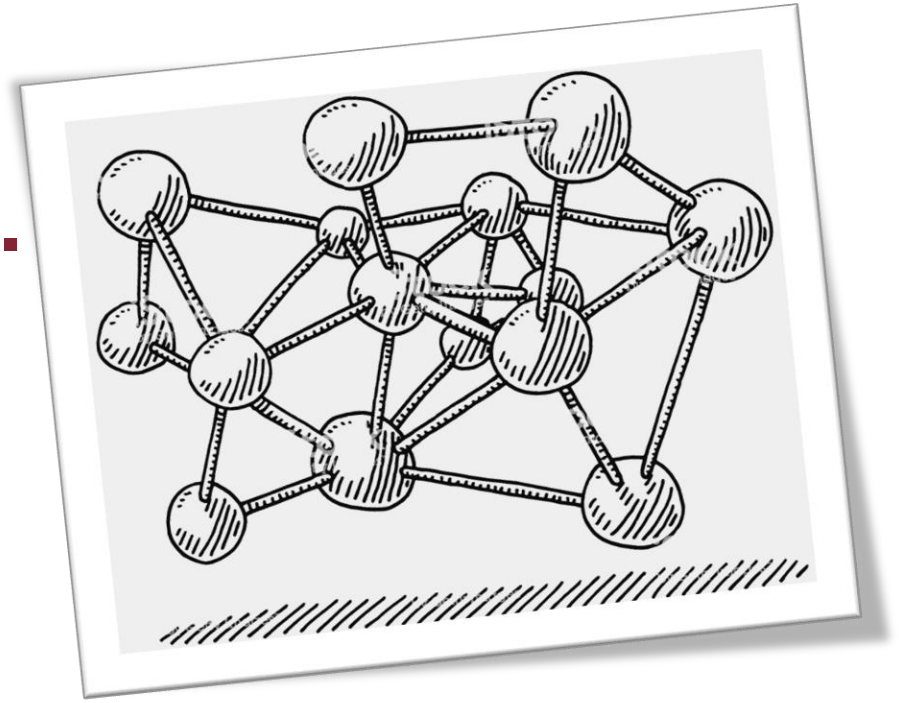
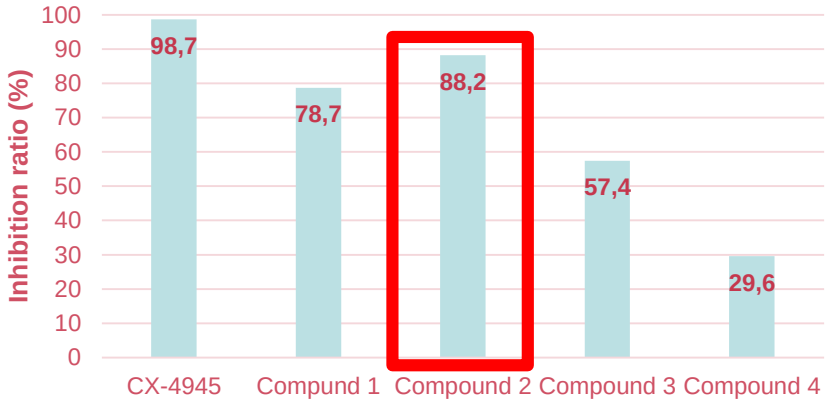


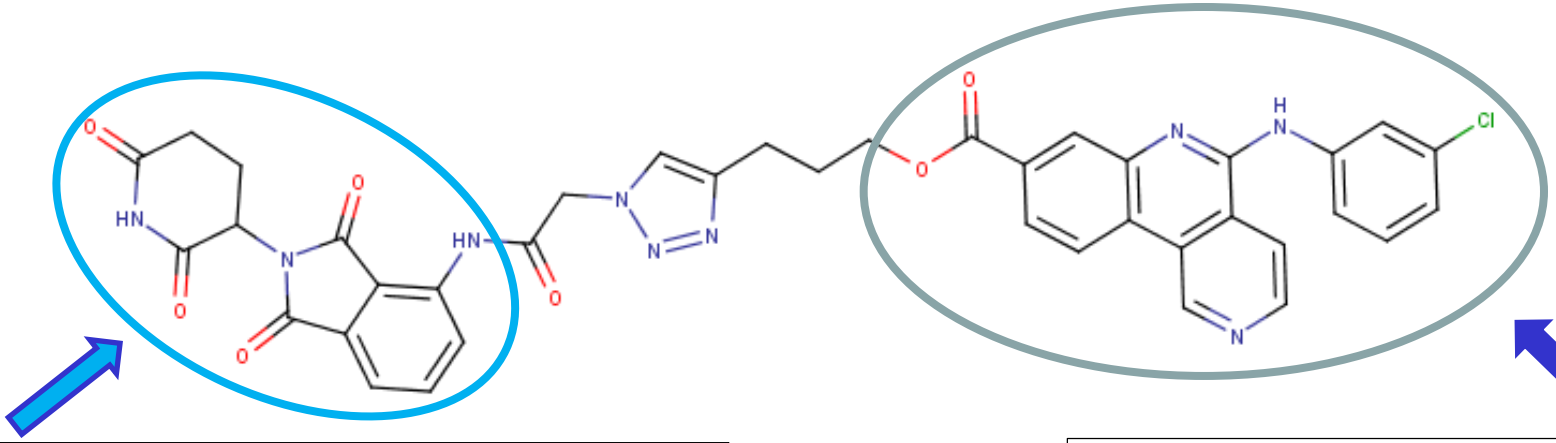
3. PROTACs: Compound 2

Bioorganic Chemistry
Volume 81, December 2018, Pages 536-544

Chemically induced degradation of CK2 by proteolysis targeting chimeras based on a ubiquitin–proteasome pathway

Hong Chen [1], Feihong Chen [1], Nannan Liu, Xinyi Wang, Shaohua Gou





degradation machinery-recruiting portion

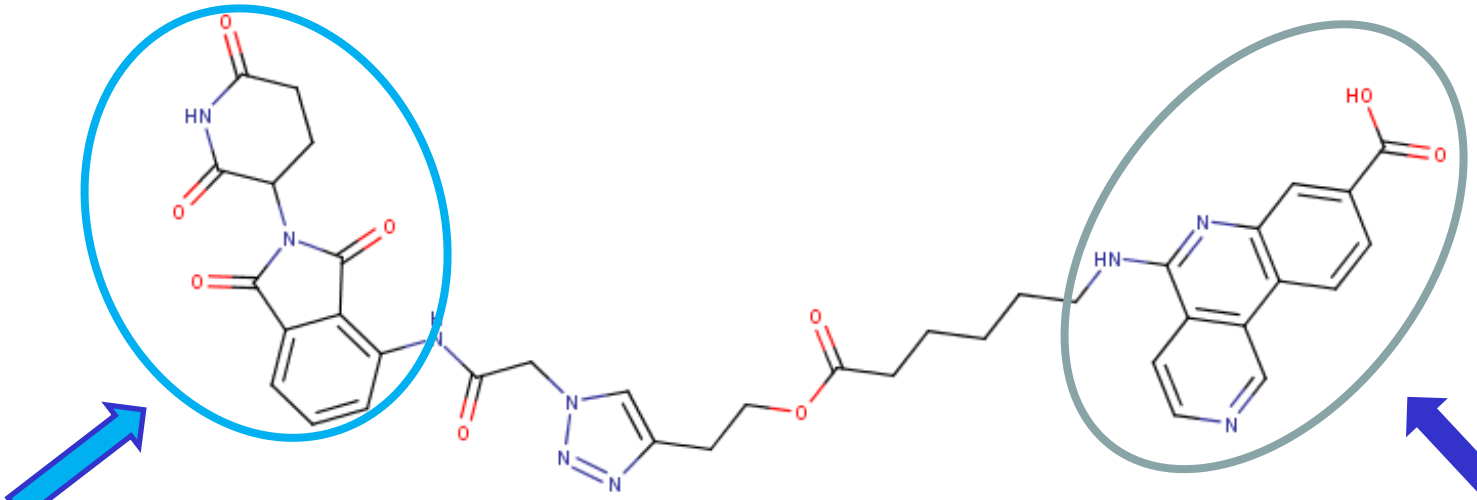
target protein-binding moiety

Chen, H., Chen, F., Liu, N., Wang, X. & Gou, S. Chemically induced degradation of CK2 by proteolysis targeting chimeras based on a ubiquitin–proteasome pathway. *Bioorg. Chem.* **81**, 536–544 (2018).

3. PROTACs: compound V-LRY715

❖PROTAC V-LRY715 is structurally similar to that of *Chen, H. et al.*[5]

verify if there is a more stable interaction that can promise a greater activity.

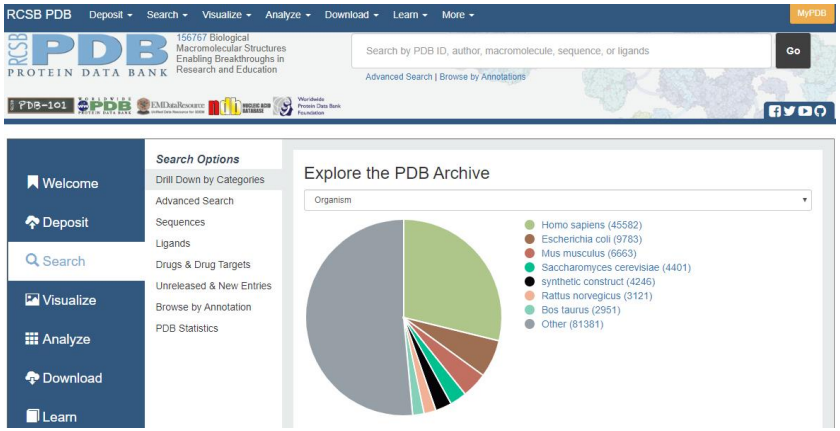


degradation machinery-recruiting portion

target protein-binding moiety

3. Workflow

1.



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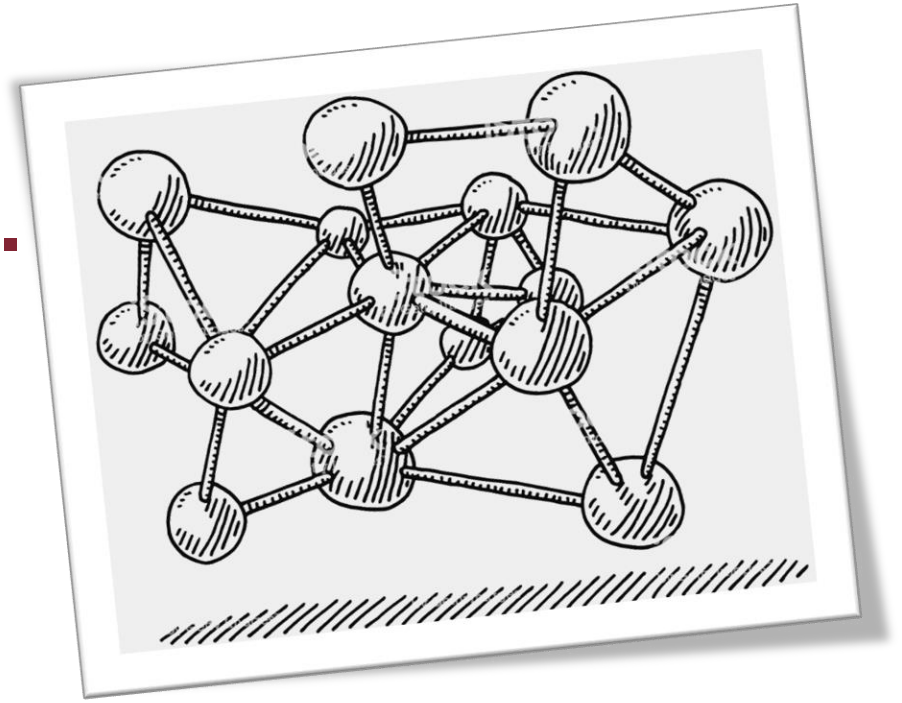
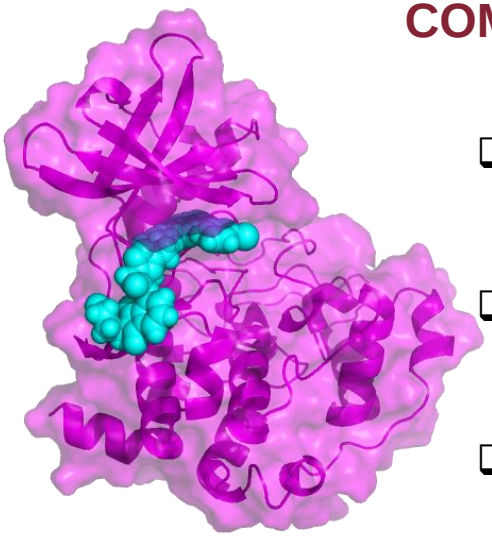


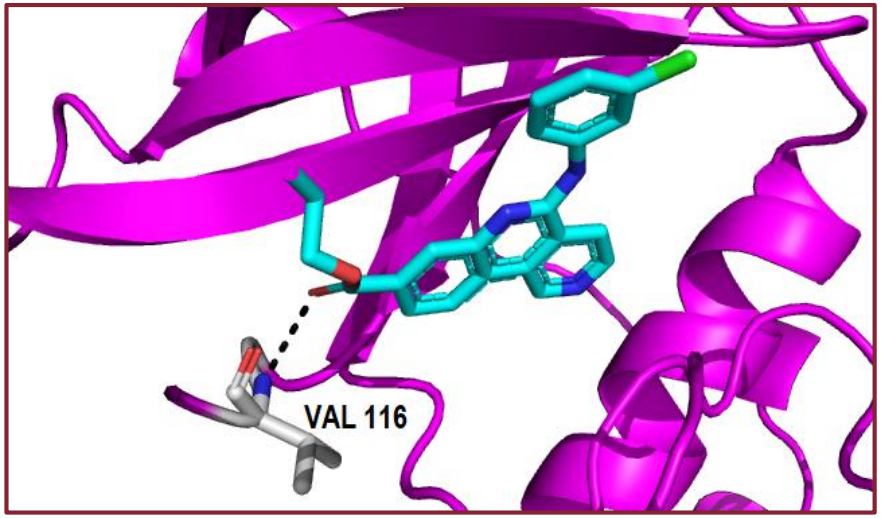
3.

STUDY OF COMPOUND 2: molecular docking

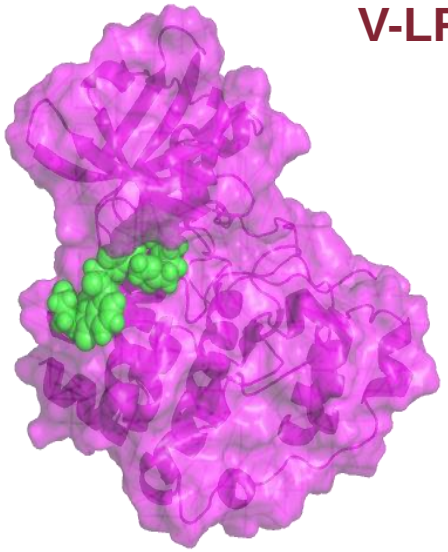
COMPOUND 2



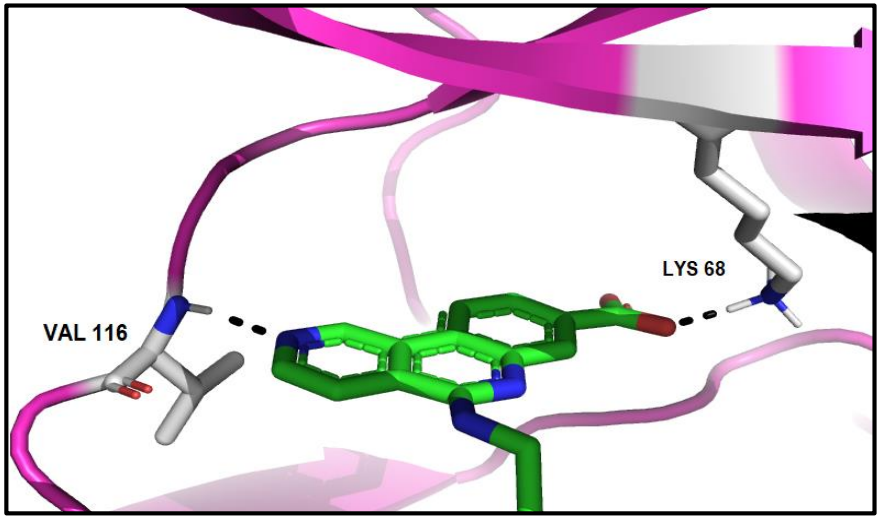
- docking score of -**11.504 kcal/mol**.
- Lack ionic interaction with Lys68.
- Respected interaction with hinge region

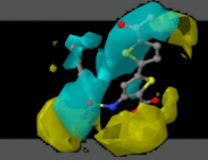


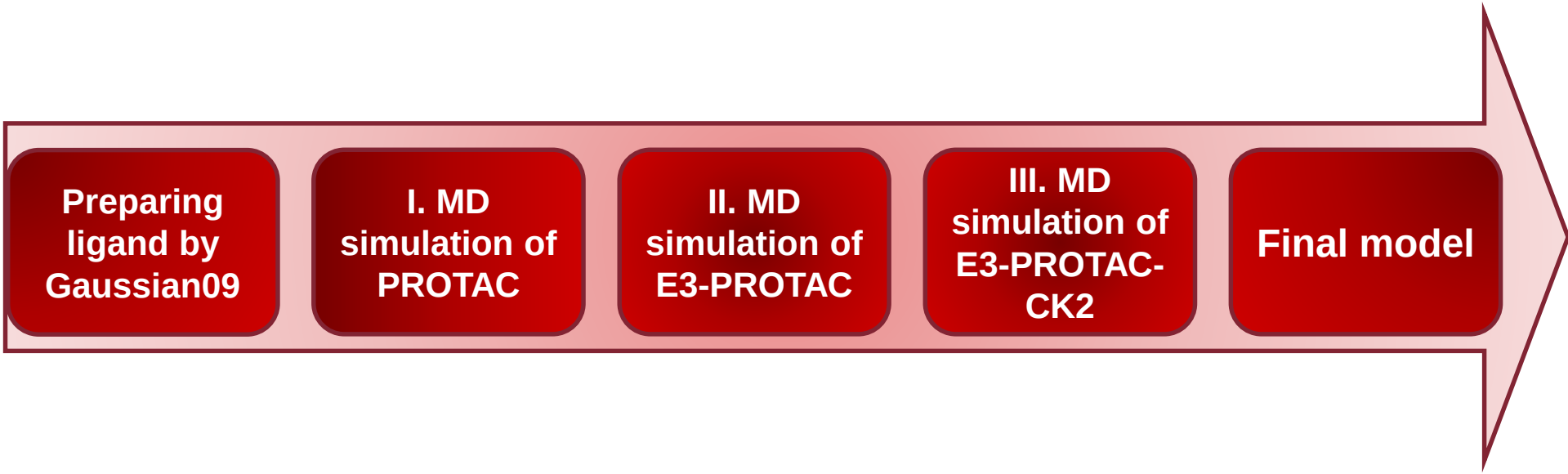
V-LRY715



- docking score of -**14.393 kcal/mol**.
- Bonds both with Val116 of hinge region and side chain of Lys68






Preparing ligand by Gaussian09
I. MD simulation of PROTAC
II. MD simulation of E3-PROTAC
III. MD simulation of E3-PROTAC-CK2
Final model

Preparing ligand by Gaussian09

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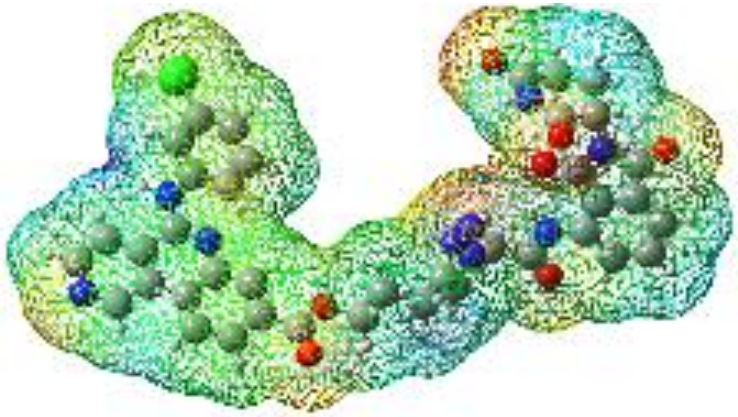
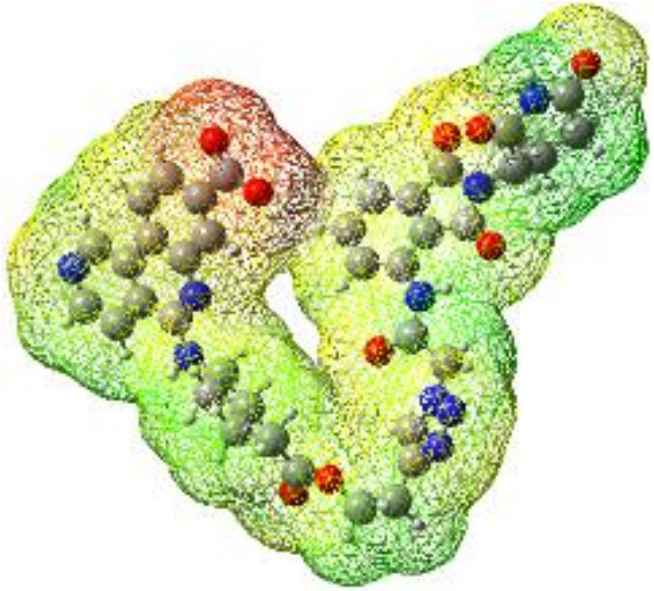
III. MD simulation of E3-PROTAC-CK2

Final model

COMPOUND 2



V-LRY715



Preparing ligand by Gaussian09

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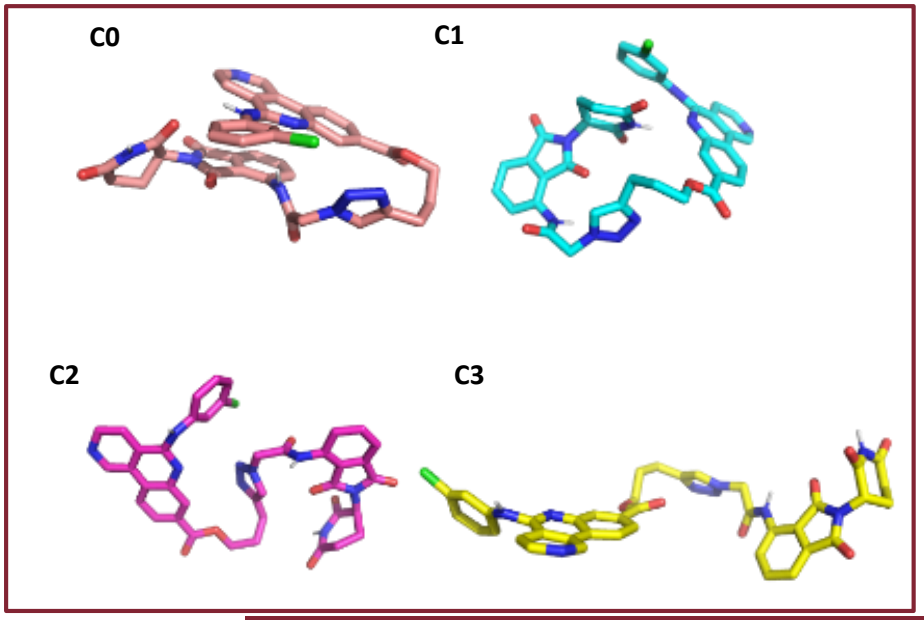
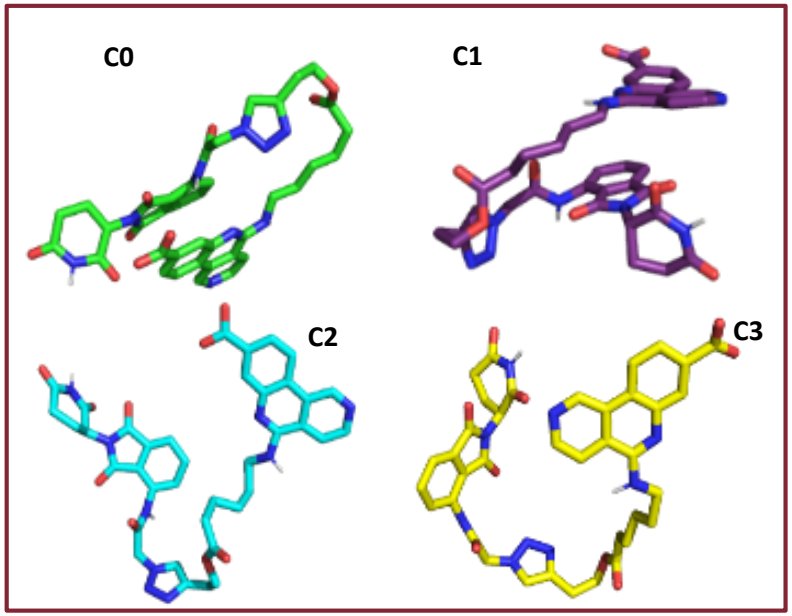
Final model

COMPOUND 2



V-LRY715



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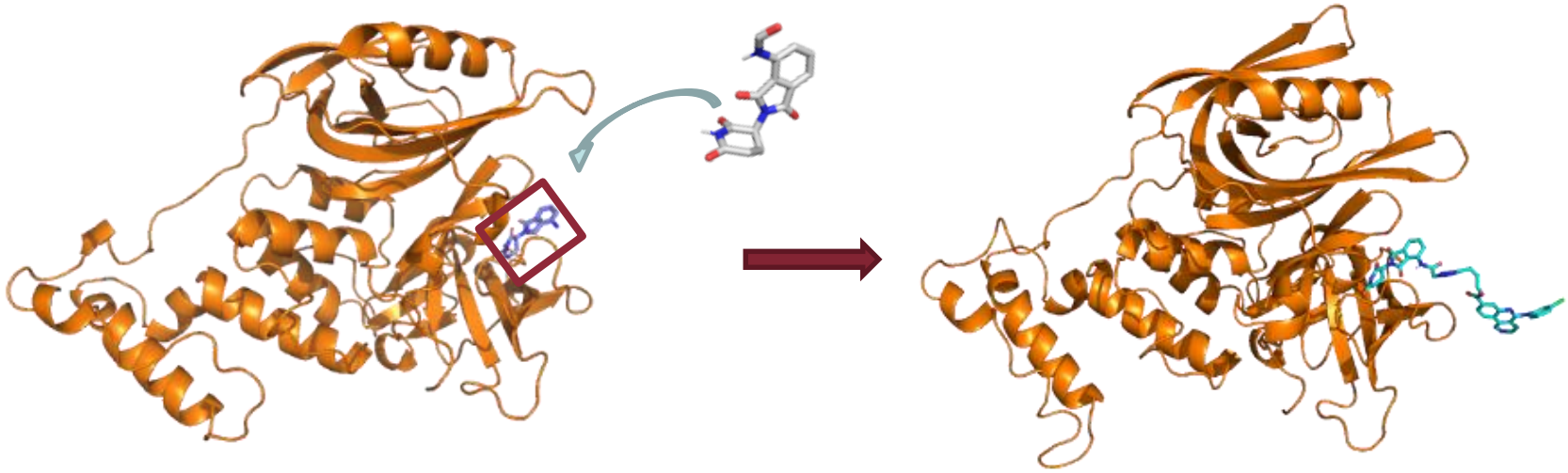

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Final model

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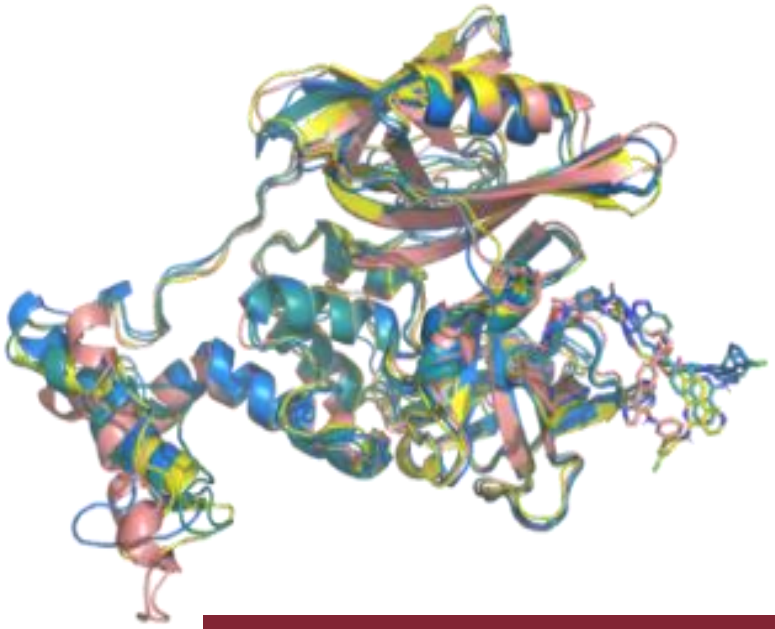

V-LRY715

Preparing ligand by Gaussian09

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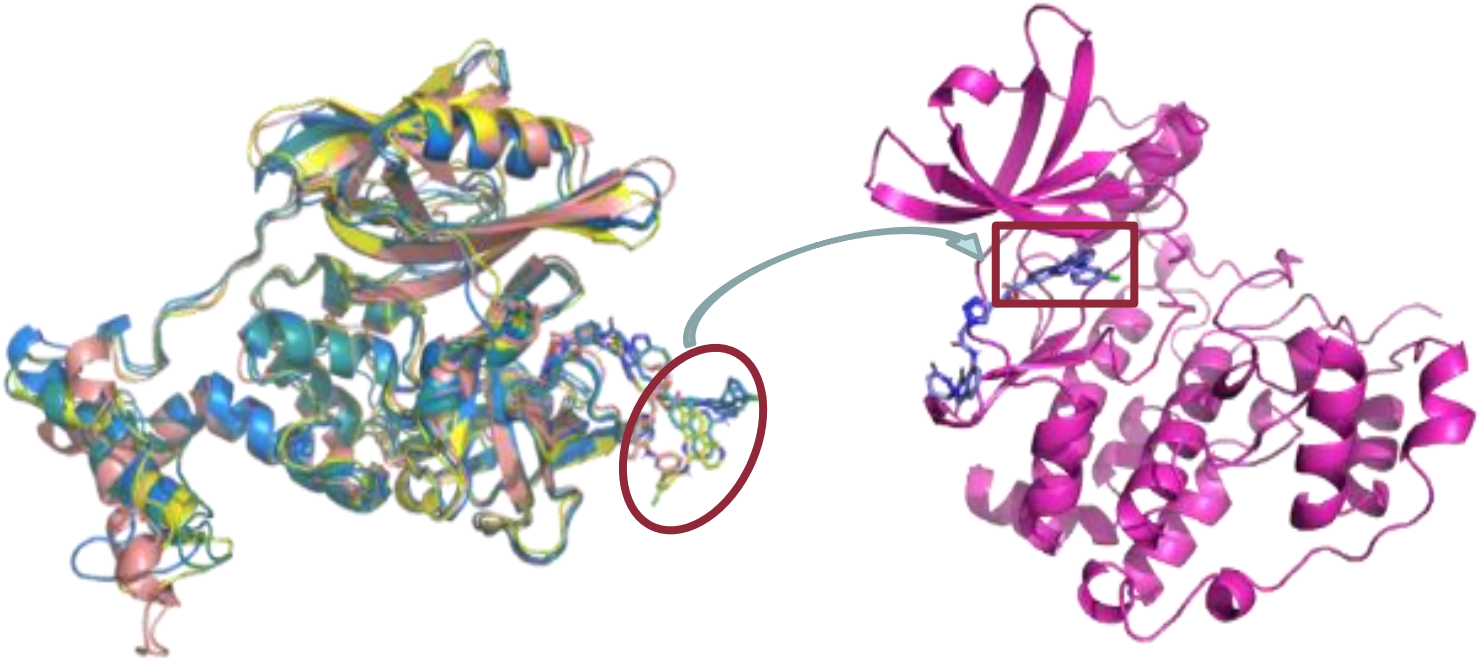
Final model

COMPOUND 2



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Final model

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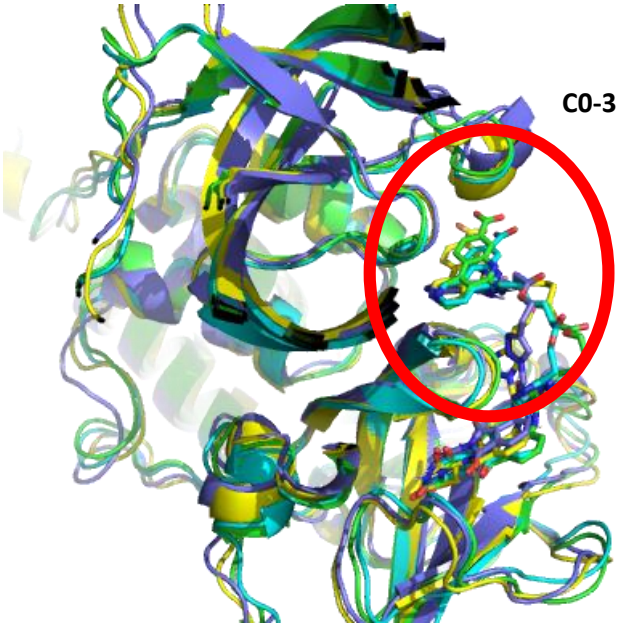
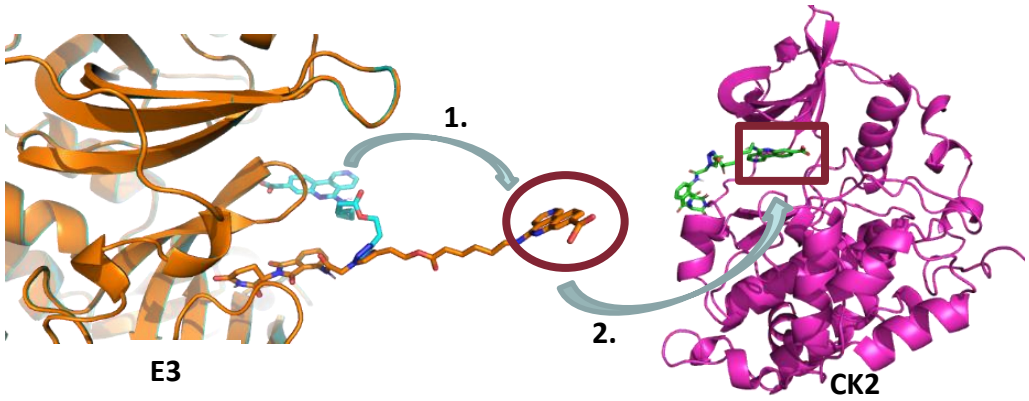
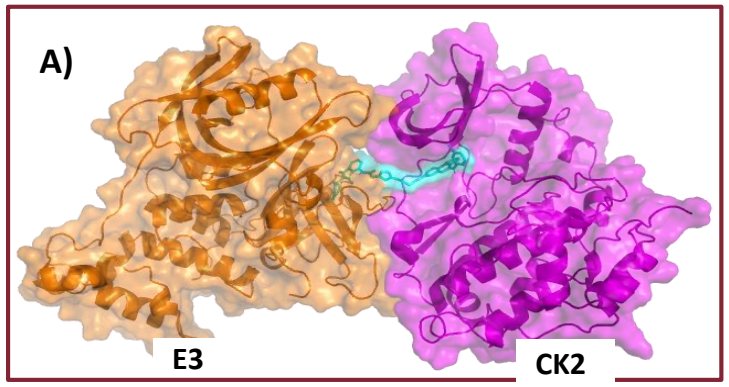
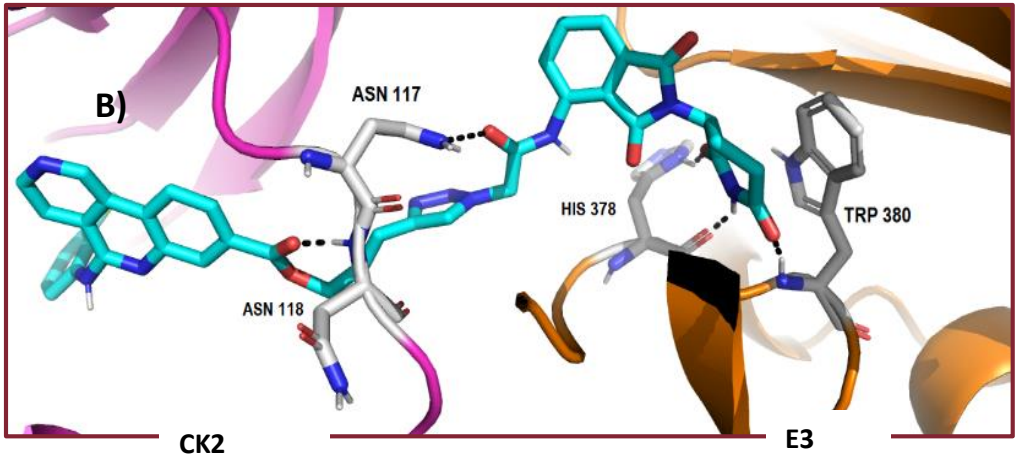


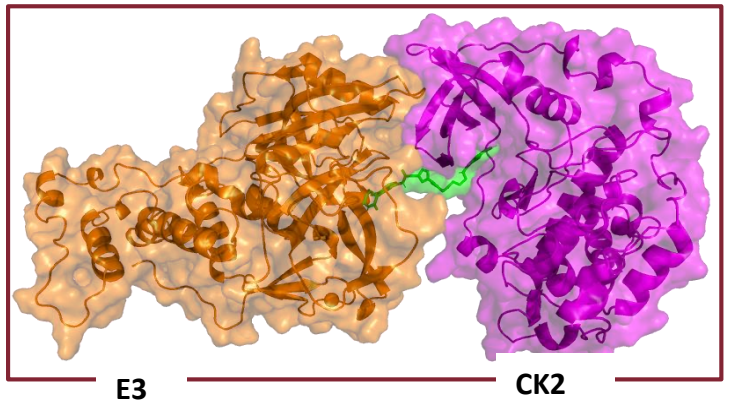


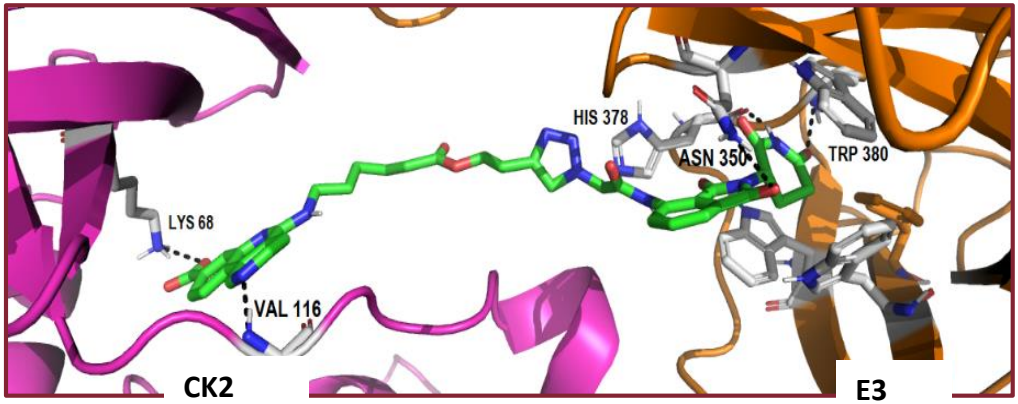




COMPOUND 2

V-LRY715

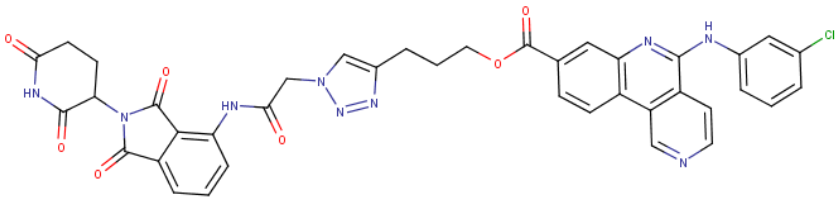




COMPARATION:

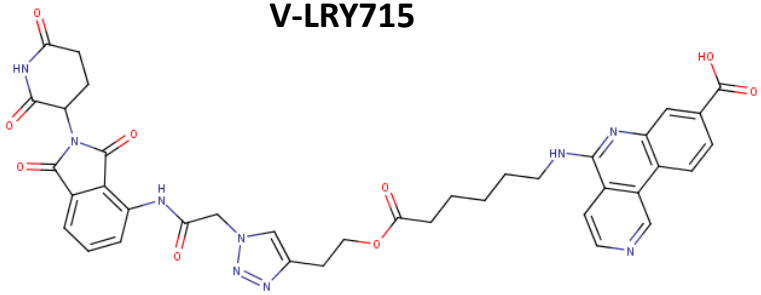
V-LRY715 vs compound2

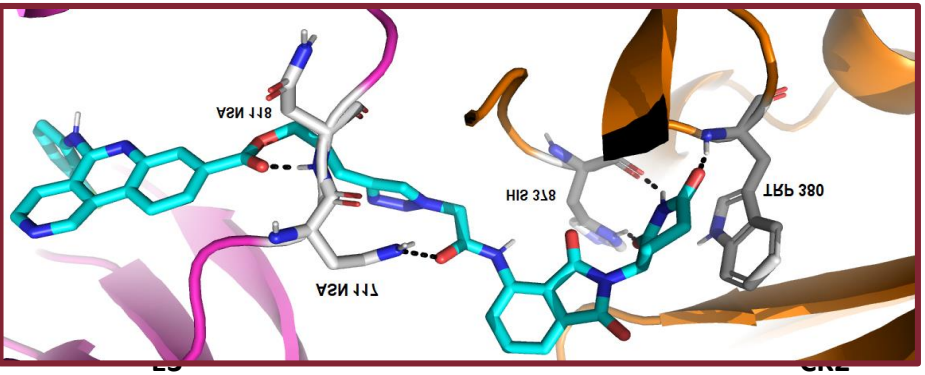
Compound 2

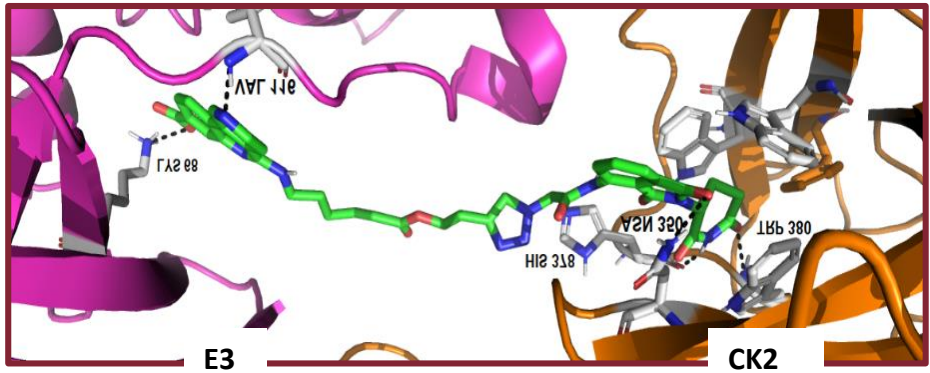


VS

V-LRY715







E3 CK2

STUDY OF COMPOUND 2: results

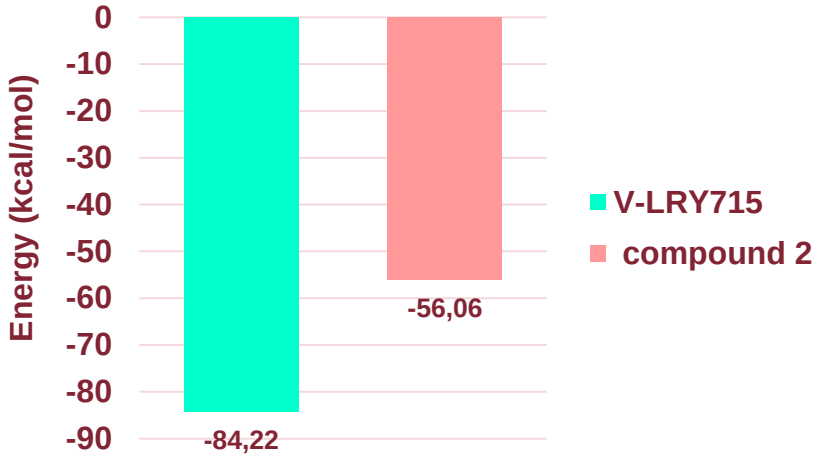
COMPOUND 2

INTERACTION	MEAN
ELE	-5.71
VDW	-54.21
SUR	-2.86
DESOL-REC	3.86
DESOL-LIG	6.39
H-BOND	-3.53
TOT	-56.06

V-LRY715

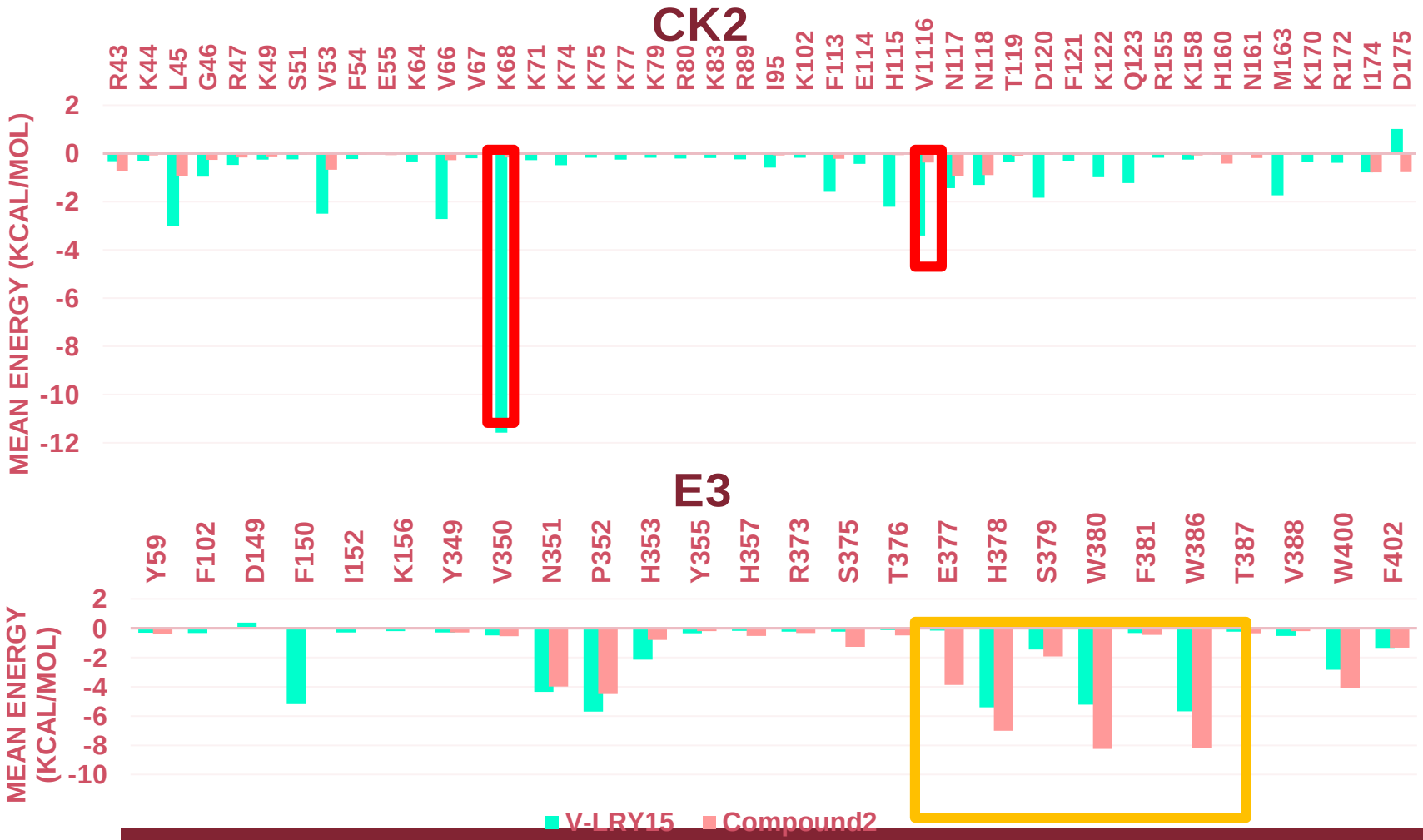
INTERACTION	MEAN
ELE	-18.48
VDW	-87.93
SUR	-5.63
DESOL-REC	9.16
DESOL-LIG	21.45
H-BOND	-2.79
TOT	-84.22

Comparison of total energies

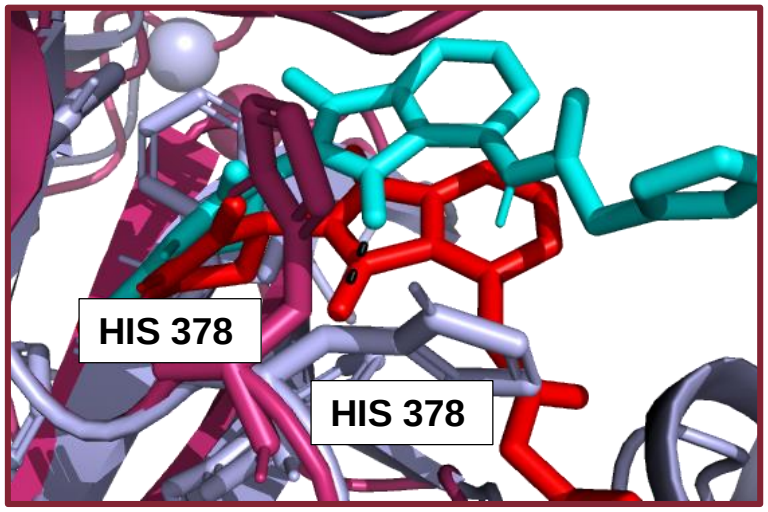


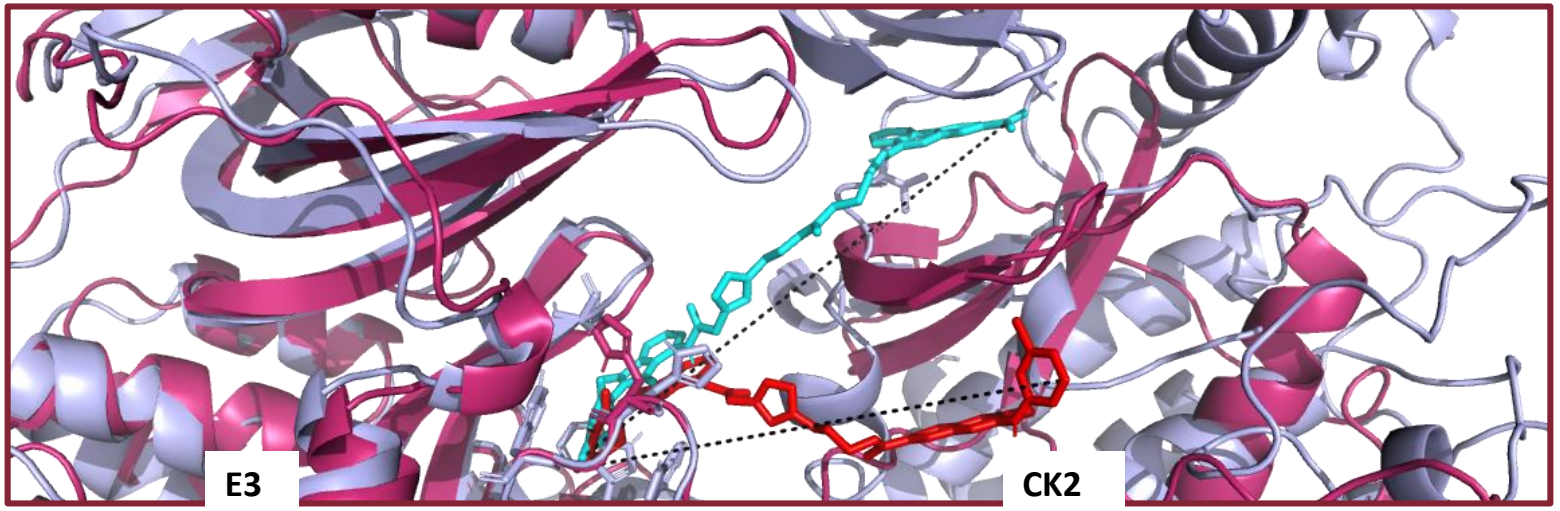
COMPARATION:

V-LRY715 vs compound2



COMPARATION:
V-LRY715 vs compound2

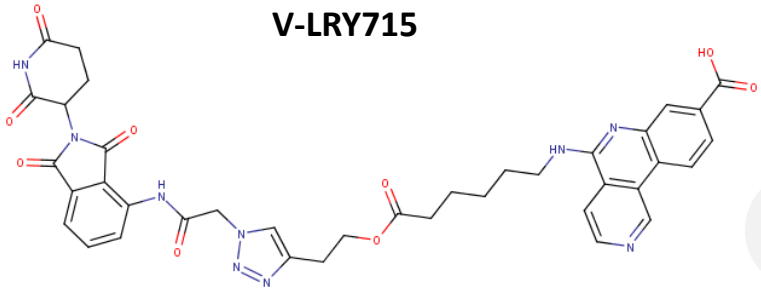




COMPARATION:

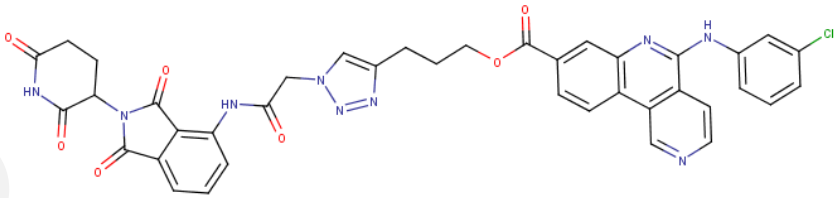
V-LRY715 vs compound2

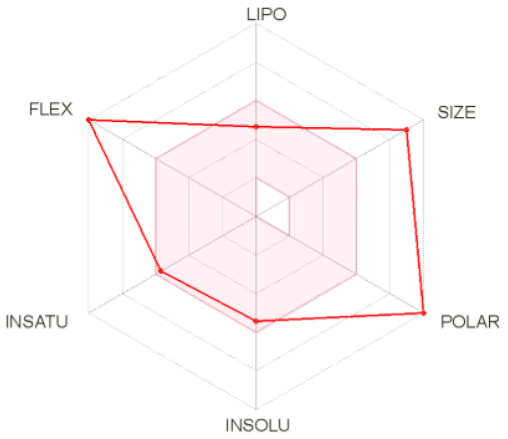
V-LRY715

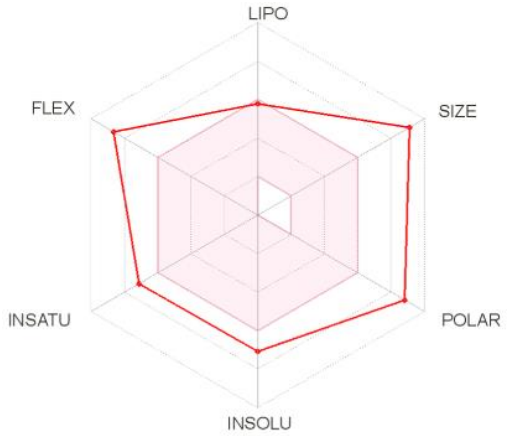


vs

Compound 2







Molecule	MW	Fraction Csp3	Rotatable bonds	TPSA	XLOGP3	ESOL Log S
V-LRY715	761.74	0.29	17	244.77	2.63	-5.43
Compound **2**	772.16	0.18	13	207.47	4.6	-7.08

CONCLUSIONS

We have proposed a plausible binding-mode for the interaction of compound **2** reported by *Chen et al.* and the E3-ligase and CK2.

We have designed a new PROTAC that to guarantees the fundamental interactions of the CX-4945 moiety with Val116 and Lys68.

We have carried out a comparative study of the binding energies and can state that the proposed V-LRY715 can be a better CK2-binding agent than compound **2**.

New PROTACs with a shorter linker both to simplify the synthesis and to reduce the flexibility of the molecule trying to reduce the number of routable bonds and finally with the intent of bringing the two proteins to favour a good protein interaction and make the complex more stable.

NEW PROTACs PROPOSED

- Analogous to V-LRY175 with a shorter linker
- In order to both simplify the synthesis and to reduce the flexibility of the molecule trying to reduce the number of routable bonds.

TBB is thought as new probable moiety to recruit CK2:

Although the TBB shows less enzyme activity compared to CX-4945TBB has a very simple synthetic process