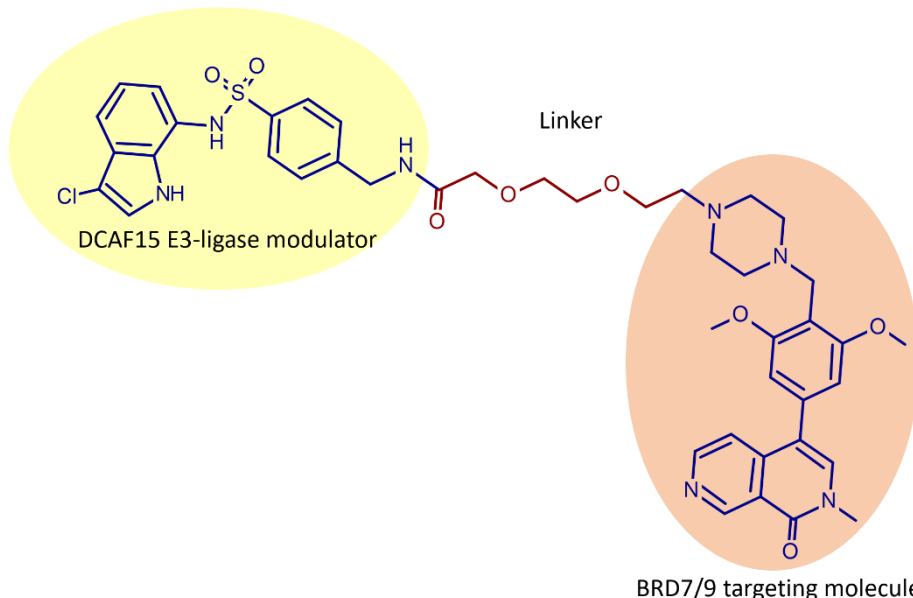


PROTAC Analysis tool



The PROTAC analysis tool breaks up PROTAC-molecules into their constituent parts. The algorithm identifies the linker that joins the two ligands. It compares the ligands against a known list of PROTAC modulators to identify the E3 ligase modulator as 'R1' positions it on the left side of molecule, extends the linker horizontally in the middle of the molecule, and identifies the remaining ligand as the warhead ('R2') placing on the right-hand side of the molecules. Using **SARvision/SM**, molecules can be readily browsed, filtered and molecule properties calculated. In a

folder name 'R1' in the scaffold tree, the user can add any new or proprietary E3 ligase molecules that the algorithm is not identifying by placing into the 'R1' column.

1. Open a set of PROTAC molecules for study (file->open sdf or project file).

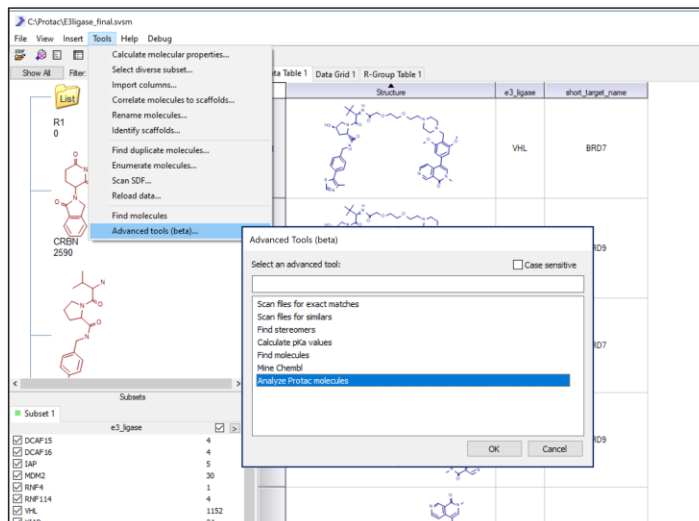
The screenshot shows the PROTAC Analysis tool interface. The main window displays a list of molecules with columns for 'Structure', 'e3_ligase', and 'short_target_name'. The 'e3_ligase' column is highlighted with a red box, and a filter is applied to it. The filter is set to 'Filter: column data'.

Structure	e3_ligase	short_target_name
	VHL	BRD7
	VHL	BRD9
	VHL	BRD7
	VHL	BRD9
	CRBN	BRD9
	CRBN	BRD9

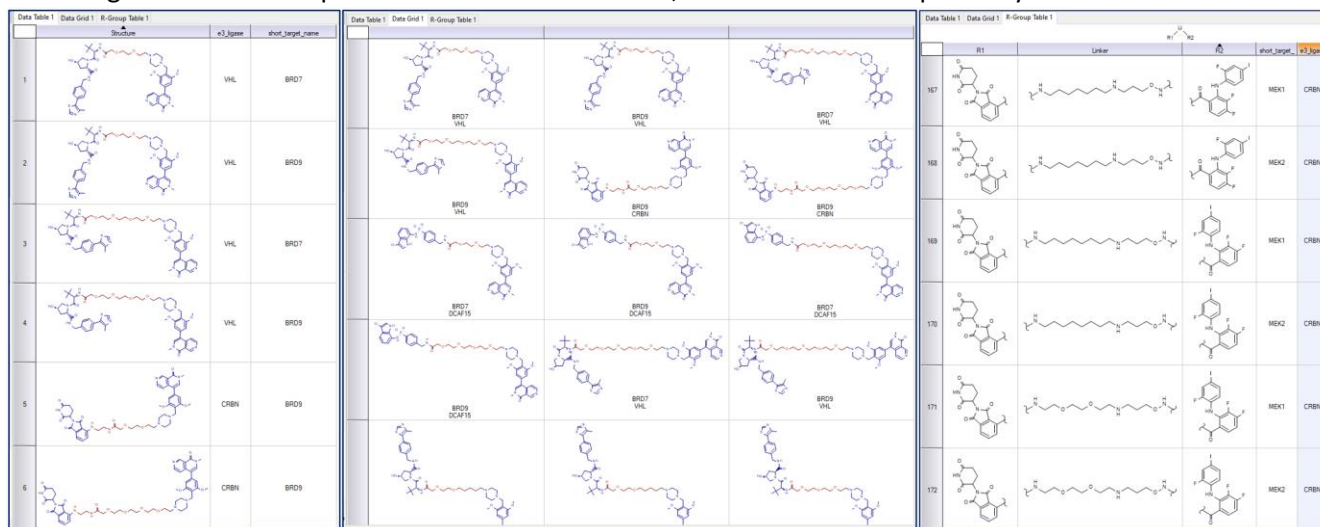
The 'e3_ligase' filter list shows the following items:

- DCAF15 (4)
- DCAF16 (4)
- IAP (5)
- MEHQ2 (30)
- RNF4 (1)
- RNF114 (4)
- VHL (1152)
- XIAP (34)
- cIAP1 (122)

2. Under tools->Advanced tools->Analyze PROTACs implements an algorithm to break PROTACs into their constituent parts. This should process ~400 molecules a second...give a few seconds.



3. Three different table views of the data. The E3 ligase modulator is oriented on the right, the linker should be extended horizontally in the middle and identified in red, and the warhead or targeting ligand should be located on the right. In the R-Group Table these are labeled 'R1', 'Linker' and 'R2' respectively.



4. Calculate property columns for entire PROTAC and for each part of the molecule:Tools->Calculate molecular properties.

The screenshot shows the PROTAC Analysis Tool interface. A table displays molecular data for various targets and linkers. A dialog box titled "Calculate Molecular Properties" is open, allowing users to select properties to calculate for the molecules in the table.

short_target_name	e3_ligase	TPSA(dckl)	Linker - TPSA(dckl)	R2 - TPSA(dckl)
FLT3	CRBN	274.8	274.8	274.8
CDK2	CRBN	276.7	276.7	276.7
JAK1	XAP	196.5	196.5	196.5
JAK2	XAP	196.5	196.5	196.5
JAK1	VHL	188.5	188.5	188.5

The "Calculate Molecular Properties" dialog box lists the following properties to be calculated:

- Num of H-bonds
- Num of Heavy Atoms
- Num of Rings
- Complexity Index
- SMILES
- logP(dckl)
- TPSA(dckl)
- SA(wa)(dckl)
- MR(dckl)
- HKA(dckl)

5. Filter by E3 ligase or any column of data in the dataset.

The screenshot shows the PROTAC Analysis Tool interface with a filtered dataset. The "e3_ligase" column is highlighted in blue, indicating that the data is filtered by this column. The "Subsets" panel on the left shows the filter applied: "e3_ligase".

R1	Linker	R2	short_target_name	e3_ligase	TPSA(dckl)	R1 - TPSA(dckl)	Linker - TPSA(dckl)	R2 - TPSA(dckl)
1			BRD7	DCAF15	169.3	169.3	169.3	169.3
2			BRD9	DCAF15	169.3	169.3	169.3	169.3
3			BRD7	DCAF15	187.8	187.8	187.8	187.8
4			BRD9	DCAF15	187.8	187.8	187.8	187.8

The "Subsets" panel shows the following filter applied:

- e3_ligase 4
- DCAF15 4
- DCAF16 5
- IAP 30
- MDM2 1
- RNF4 4
- RNF114 1152
- VHL 34
- XIAP 122
- cIAP1