1 PLIP Command Line Tool

1.1 Setup

PLIP is written in Python and has the following dependencies (python packages) to run properly:

- lxml
- openbabel $\geq$ 2.3.2
- pybel
- numpy
- pymol $\geq$ 1.7

Imagemagick is optional for PLIP, but is used to scale the output images.

1.2 Input and Options

The program can be used on any PDB file from the PDB archive (online) or output files from other tools in PDB format without further preparation. To analyze a structure from your machine, run

```
python plip-cmd.py -f <file.pdb>
```

To fetch and analyze a structure from the PDB archive (requires internet connection), run PLIP using

```
python plip-cmd.py -i <4-letter-PDB-ID>
```

Several options are available, which are shown by calling the help message with

```
python plip-cmd.py -h
```

`-h, -help`	Shows help message
`-f INPUT, -file INPUT`	Read in a file in PDB format
`-i PDBID, -input PDBID`	Fetch and analyze a file from the online PDB archive
`-o OUTPATH, -out OUTPATH`	Sets the output folder for PLIP result files (standard: working directory)
`-v, -verbose`	Sets verbose mode
`-p, -pics`	Generate ray-traced pictures
`-x, -xml`	Generate XML format reports
`-y, -pymol`	Generate PyMOL session files
`-maxthreads`	Max. number of simultaneously processed binding sites

Setting maxthreads to 0 will deactivate multiprocessing. By default, parallel processing is turned off for usage on Windows.

2 Validation

For the validation of the PLIP algorithm we composed a set of 30 diverse protein-ligand complexes with non-covalent interactions described in literature. The validation cases (Table 3) cover all interaction types detectable with PLIP and structures with different resolutions (1.2 to 3.3 Å). To implement the tests, the set of interacting residues for a specific interaction type was compared against the set PLIP detects for the given complex. Contact both reported in literature and detected with PLIP are listed as *true positives*. Additional contacts detected by PLIP, but not listed in the publication are labeled as *false positives*. During testing, initial thresholds from literature have been modified (in the case of distance thresholds max. $\pm$ 1 Å) in order to prevent false negative results. False negative contacts still listed in Table 3 have been checked manually. They either result from errors in the publication, different interpretation of contact (as often the case for types with similar characteristics as salt bridges and hydrogen bonds), or unreasonable thresholds.

3 PLIP Algorithm

PLIP uses a rule-based system for detection of non-covalent interactions between protein residues and ligands. Information on chemical groups able to participate in a specific interaction (e.g. requirements for hydrogen bond donors) and interaction geometry (e.g. distance and angle thresholds) from literature are used to detect characteristics of non-covalent interactions between contacting atoms of protein and ligands. For each binding site, the algorithm searches first for atoms or atom groups in the protein and ligand which could possibly be partner in specific interactions. Subsequently, geometric rules are applied to match groups in protein and ligand forming an interaction.

Previous to the detection step for the interactions, PLIP extracts all ligands contained in the structure. Ions, DNA, modified amino acids, preparation artifact and solvent components are blacklisted as ligands. The complete list used for the filtering step is available on our website. Additionally, we use the BioLiP ([1]) list of possible artifacts to remove ligands which are in this list and appear 10 times or more in a structure.

4 Detection of functional groups, atoms or molecules

4.1 Binding site atoms

The binding site distance cutoff is determined by adding up `BS_DIST_MAX` to the maximum extent of the ligand (maximum distance of a ligand atom to ligand centroid). All protein atoms within this distance cutoff to any binding site atoms are counted as belonging to the binding site.

4.2 Hydrophobic Atoms

An atom is classified as *hydrophobic* if it is a carbon and has only carbon or hydrogen atoms as neighbours.

4.3 Aromatic Rings

OpenBabel is used to identify rings (SSSR perception) and their aromaticity. In cases where no aromaticity is reported by OpenBabel, the ring is checked for planarity. To this end, the normals of each atom in the ring to its neighbors is calculated. The angle between each pair of normals has to be less than `AROMATIC_PLANARITY`. If this holds true, the ring is also considered as aromatic.

4.4 Hydrogen Bond Donors and Acceptors

OpenBabel [2] is used to identify hydrogen bond donor and acceptor atoms. Halogen atoms are excluded as hydrogen bond acceptors.

4.5 Charged Groups

The detection of charged groups is only exhaustive for the binding site, not the ligand. For proteins, positive charges are attributed to the side chain nitrogens of Arginine, Histidine and Lysine. Negative charged are assigned to the carboxyl groups in Aspartic Acid and Glutamic Acid.

In ligands, positive charges are assigned to quaterny ammonium groups, tertiary amines (assuming the nitrogen could pick up a hydrogen and thus get charged), sulfonium and guanidine groups. Negative charges are reported for phosphate, sulfonate, sulfonic acid and carboxylate.

4.6 Halogen bond donors and acceptors

Assuming that halogen atoms are not present in proteins (unless they are artificially modified), halogen bond donors are searched for only in ligands. All fluorine, chlorine, bromide or iodine atoms connected to a carbon atom qualify as donors. Halogen bond acceptors in proteins are all proximal oxygen, nitrogen or sulfur atoms connected to carbon, nitrogen, phosphor or sulfur atoms.

4.7 Water

Water atoms are assigned to a ligand-binding site complex if their oxygen atoms are within a certain cutoff to the ligand. The cutoff is determined by adding up `BS_DIST_MAX` value to the maximum extent to the ligand (maximum distance of a ligand atom to ligand centroid). This means the farthest distance of a ligand to a water atom is `BS_DIST_MAX`.

5 Detection of Interactions

For an overview on geometric cutoffs used for the prediction of interactions, see Table 1.

5.1 Hydrophobic Interactions

5.1.1 Detection Step

As hydrophobic interactions result from entropic changes rather than attractive forces between atoms, there are no clear geometries of hydrophobic association. The observed attraction

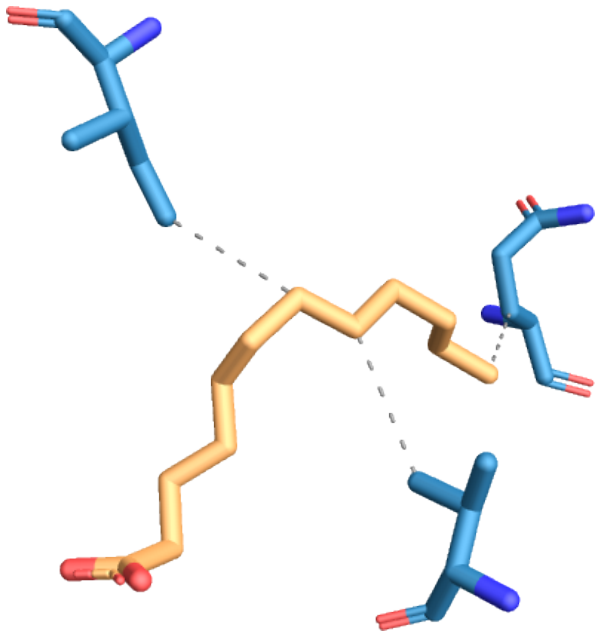

Figure 1: Hydrophobic interactions between HNF4 alpha ligand binding domain and lauric acid (1M7W:DAO-A-700)

between hydrophobic atoms decays exponentially with the distance between them [3]. A generous cutoff was chosen, identifying a prime set of hydrophobic interactions between all pairs of hydrophobic atoms within a distance of `HYDROPH_DIST_MAX`.

5.1.2 Reduction Step

Since the number of hydrophobic interactions with such an one-step approach can easily surpass all other interaction types combined, it may strongly influence subsequent evaluation or interaction fingerprinting. To overcome this problem, the number of hydrophobic interactions is reduced in several steps. First, hydrophobic interactions between rings interacting via π-stacking are removed. This is done because stacking already involves hydrophobic interactions [4]. Second, two clustering steps are applied. If a ligand atom interacts with several binding site atoms in the same residue, only the interaction with the closest distance is kept. Subsequently, the set of hydrophobic interactions is checked from the opposite perspective: if a protein atom interacts with several neighboring ligand atoms, just the interaction with the closest distance is kept. Together, these reduction steps help to report only the most representative hydrophobic interactions.

5.2 Hydrogen Bonds

5.2.1 Detection Step

A hydrogen bond between a hydrogen bond donor and acceptor (subsection 4.4) is reported if several geometric requirements are fulfilled. The distance has to be less than `HBOND_DIST_MAX` and the angle at the donor group (D-H...A) above `HBOND_DON_ANGLE_MIN`.

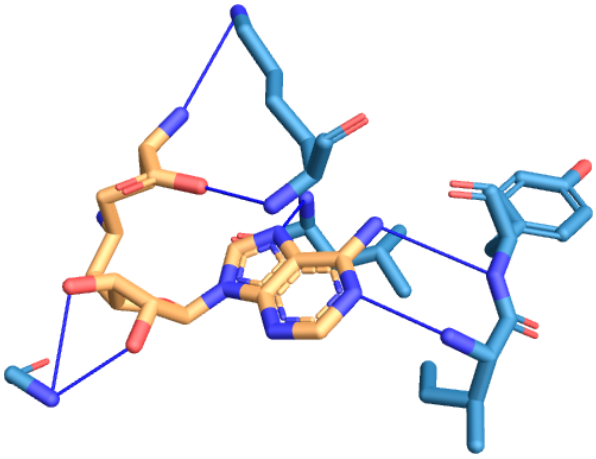

Figure 2: Hydrogen bonds between *M. jannaschii* Nep1 and Sinefungin (3BBH:SFG-A-206)

5.2.2 Reduction Step

Since salt bridges involve purely electrostatic interactions as well as hydrogen bonds [5], it is not meaningful to report both interaction types between the same groups. Thus, hydrogen bonds between atoms are removed if they belong to groups that already form a salt bridge to that atom. As a general rule, a hydrogen bond donor can take part in only one hydrogen bond, while acceptor atoms can be partners in multiple hydrogen bonds (e.g. bifurcated hydrogen bonds). For multiple possible hydrogen bonds from one donor, only the contact with the donor angle closer to 180 °is kept.

5.3 Aromatic stacking

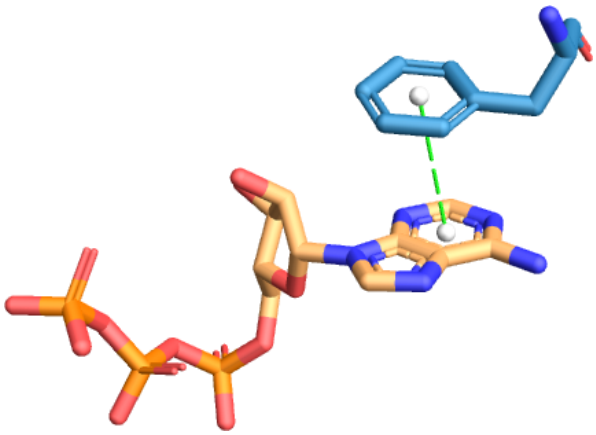

Figure 3: Aromatic stacking between *Trypanosoma brucei* RNA editing ligase 1 and ATP (1XDN:ATP-A-501)

π-stacking for two aromatic rings is reported whenever their centers are within a distance of `PISTACK_DIST_MAX` [6], the angle deviates no more than `PISTACK_ANG_DEV` from the optimal angle of 90° for T-stacking or 180° for P-stacking. Additionally, each ring center is projected

onto the opposite ring plane. The distance between the other ring center and the projected point (i.e. the offset) has to be less than `PISTACK_OFFSET_MAX`. This value corresponds approximately to the radius of benzene + 0.5 Å.

5.4 Pi-cation interactions

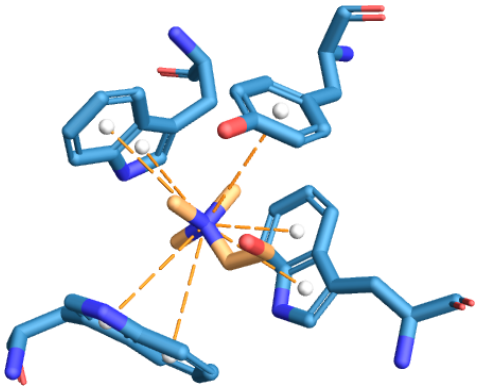

Figure 4: Pi-cation interactions between ABC-transporter choline binding protein and choline (2REG:CHT-A-1)

π-cation interactions are reported for each pairing of a positive charge and an aromatic ring if the distance between the charge center and the aromatic ring center is less than `PICATION_DIST_MAX` [7]. In the case of a putative π-cation interaction with a tertiary amine of the ligand, an additional angle criterion is applied (see documentation in the source code).

5.5 Salt Bridges

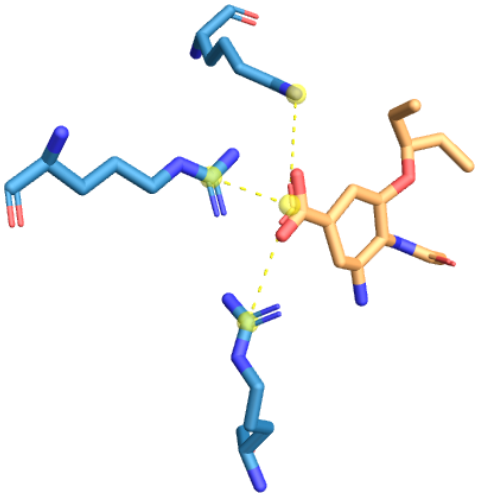

Figure 5: Salt bridges between Shanghai N9 neuraminidase and oseltamivir carboxylate (4MWW:G39-A-513)

Whenever two centers of opposite charges come within a distance of `SALTBRIDGE_DIST_MAX`,

a salt bridge is reported [8]. In contrast to hydrogen bonds, there are no additonal geometric restrictions.

5.6 Water-bridged hydrogen bonds

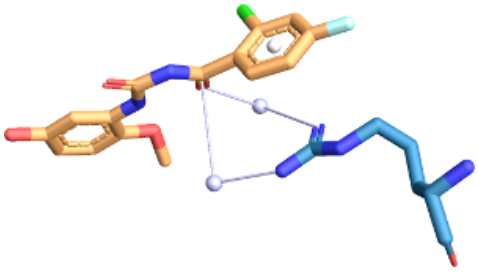

Figure 6: Water-bridged hydrogen bonds between human liver glycogen phosphorylase and acyl urea inhibitor (2ATI:IHU-A-848)

5.6.1 Detection Step

While residues can be bridged by more than one water molecule, for the prediction in this script the only case considered is one water molecule bridging ligand and protein atoms via hydrogen bonding. The water molecule has to be positioned between hydrogen bond donor/acceptor pairs of ligand and protein with distances of the water oxygen within `WATER_BRIDGE_MINDIST` and `WATER_BRIDGE_MAXDIST` to the corresponding polar atoms of the donor or acceptor groups. If a constellation with a water atom fulfills these requirements, two angles are checked. The angle ω between the acceptor atom, the water oxygen and donor hydrogen has to be within `WATER_BRIDGE_OMEGA_MIN` and `WATER_BRIDGE_OMEGA_MAX`. Additionally, the angle θ between the water oxygen, the donor hydrogen and the donor atom has to be larger than `WATER_BRIDGE_THETA_MIN`. The geometric constraints have been taken from [9].

5.6.2 Reduction Step

Similar to standard hydrogen bonds, a water molecule is only allowed to participate as donor in two hydrogen bonds (two hydrogen atoms as donors). In the case of more than two possible hydrogen bonds for a water molecule as donor, only the two contacts with a water angle closest to 110 °are kept.

5.7 Halogen bonds

Halogen bonds are reported for each pairing of halogen bond acceptor and donor group having a distance of less than `HALOGEN_DIST_MAX` and angles at the donor and acceptor group of `HALOGEN_DON_ANGLE` and `HALOGEN_ACC_ANGLE` with a deviation of no more than `HALOGEN_ANG_DEV`.

5.8 Currently non-supported interaction types

- Metal coordination

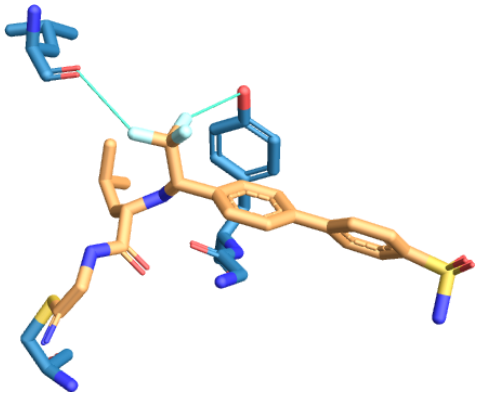

Figure 7: Halogen bonds between Cathepsin K and an inhibitor (1VSN:NFT-A-238)

- Covalent bonds
- Weak hydrogen bonds involving carbon atoms
- Halogen-Water-Hydrogen Bridges
- Water bridges of higher degree (bridging over more than one water molecule)

6 Appendix

Table 1: **Standard angle and distance thresholds** used for prediction. Angles in degree and distances in Ångström.

Variable	Value	Description	Ref.
BS_DIST_MAX	8.5 Å	Max. Cutoff for determination of binding site atoms	-
AROMATIC_PLANARITY	7.5 °	Max. Cutoff for planarity criterion in aromatic ring detection	-
HYDROPH_DIST_MAX	4.0 Å	Max. distance of carbon atoms for a hydrophobic interaction	-
HBOND_DIST_MAX	4.1 Å	Max. distance between acceptor and donor in hydrogens bonds	[10]
HBOND_DON_ANGLE_MIN	100 °	Min. angle at the hydrogen bond donor (D-H...A)	[10]
PISTACK_DIST_MAX	7.5 Å	Max. distance between ring centers for stacking	[6]
PISTACK_ANG_DEV	30 °	Max. deviation from optimum angle for stacking	-
PISTACK_OFFSET_MAX	2.0 Å	Max. offset between aromatic ring centers for stacking	-
PICATION_DIST_MAX	6.0 Å	Max. distance between charge and aromatic ring centers	[7]
SALTBRIDGE_DIST_MAX	5.5 Å	Distance between two centers of charges in saltbridges	[8]
HALOGEN_DIST_MAX	4.0 Å	Max. distance between oxygen and halogen	[11]
HALOGEN_ACC_ANGLE	120 °	Optimal halogen bond acceptor angle	[11]
HALOGEN_DON_ANGLE	165 °	Optimal halogen bond donor angle	[11]
HALOGEN_ANGLE_DEV	30 °	Max. deviation from optimal halogen bond angles	[11]
WATER_BRIDGE_MINDIST	2.5 Å	Min. distance between water oxygen and polar atom	[9]
WATER_BRIDGE_MAXDIST	4.0 Å	Max. distance between water oxygen and polar atom	[9]
WATER_BRIDGE_OMEGA_MIN	75 °	Min. angle between acceptor, water oxygen and donor hydrogen	[9]
WATER_BRIDGE_OMEGA_MAX	140 °	Max. angle between acceptor, water oxygen and donor hydrogen	[9]
WATER_BRIDGE_THETA_MIN	100 °	Min. angle between water oxygen, donor atom and hydrogen	[9]

Table 2: Abbreviations used in the textual report files and their explanation.

Abbreviation	**Explanation**
RESNR	Residue number (as in the PDB file)
RESTYPE	Amino acid type
RESCHAIN	Chain of interacting residue
DIST	Distance between interacting atoms
DIST_H-A	Distance between hydrogen and acceptor atoms
DIST_D-A	Distance between donor and acceptor atoms
DIST_A-W	Distance between acceptor and water oxygen atoms
DIST_D-W	Distance between donor and water oxygen atoms
LIGCARBONIDX	Atom ID of ligand carbon atom
PROTCARBONIDX	Atom ID of protein carbon atom
ITYPE	Identifier for interaction type
PROTISDON	True if protein is has the donor group for the interaction
DONORIDX	Atom ID of donor atom
ACCEPTORIDX	Atom ID of acceptor atom
DON_ANGLE	Angle at the donor group
WATER_ANGLE	Angle between water oxygen, donor and acceptor group
WATER_IDX	Atom ID of water atom
PROTISPOS	True if protein provides a positive charge for the interaction
LIG_GROUP	Ligand functional group
LIG_IDX_LIST	List of atom IDs from participating atoms
OFFSET	Offset from aromatic ring
PROTCHARGED	True if the protein provides a charge for the interaction
ACC_ANGLE	Angle at the acceptor group
DONORTYPE	Type of donor atom
ACC_IDX	Atom ID of acceptor atom
SIDECHAIN	True if the hydrogen bond is formed with an amino acid sidechain
LIGCOO	Coordinates of ligand interacting atom in the PDB file
PROTCOO	Coordinates of protein interacting atom in the PDB file

Table 3: Validation set for PLIP. Listing **HAL** Halogen Bonds, **HBO** H-Bonds, **HPI** Hydrophobic Interactions, **PCT** π-Cation interactions, **PST** π-Stacking, **SBR** Salt Bridges, **WAT** Water Bridges. True positives are interactions reported by PLIP and in literature. False negatives are interactions not detected by PLIP, false positives are not listed in the publication.

PDB ID	Binding Site	Ref.	TP	FP	FN
1AGL	P84-A-400	[12]	**HAL**:L145 **HPI**:T150 **WAT**:V147		
1AJC	THA-A-999	[13]	**PST**:F330,W84		
1AKU	FMN-A-150	[14]	**HBO**:T59,W60 **HPI**:W60 **PST**:Y98 **WAT**:D63,Y100		
1AY8	PLP-A-413	[15]	**HBO**:G108,T109,N194,S257 **PCT**:W140 **SBR**:K258,R266	**HBO**:S255	
1BJU	GP6-A-910	[16]	**HBO**:S190,S195 **HPI**:L99 **SPT**:H57 **WAT**:S190,V227		**HBO**:G219,D189
1BMA	0QH-A-256	[17]	**HBO**:S203, V224, Q200 **HPI**:F223, V103		
1EVE	E20-A-2001	[18]	**PCT**:F330 **PST**:W84,W279	**PST**:W121	
1H2T	7MG-Z-1152	[18]	**HBO**:R112 **PST**:Y20,Tyr43 **SBR**:D116	**HBO**:D114,R123,R127,Q133,V134 **SBR**:D114,R127	
1N7G	NDP-A-701	[19]	**HBO**:T37,G38,Q39,D40,D92,S63,L92,A115,S117,Y128,Y185,K189,H215,R220 **PST**:R60 **SBR**:R60,R61,R69,R220 **WAT**:G35,T37,G38,D40,R60,R61,S63,N66,S117,Y128,K189,R220	**WAT**:I36	**HBO**:D91
1OSN	BVP-A-500	[20]	**HBO**:Q90 **PST**:F93,F139 **SBR**:K25,R130 **WAT**:R143	**HBO**:G22	
1P5E	TBS-A-301	[21]	**HAL**:I10,L83		
1VSN	NFT-A-283	[22]	**HBO**:G66	**HBO**:Q19,C25,D61,Y67	
1XDN	ATP-A-501	[23]	**HBO**:I61,K87,V88,N92,R111		**HBO**:E86
2EFJ	37T-A-502	[24]	**HBO**:W161,S237 **PST**:Y157	**PST**:Y368	
2IUZ	D1H-A-1440	[25]	**HBO**:W137,W52,T138,W384 **PCT**:W137 **PST**:W52,W384 **WAT**:W52,W137,W384,T138	**PST**:W137	
2REG	CHT-A-1	[26]	**PCT**:W43,W90,W205,Y119 **SBR**:D45		
2W0S	BVP-B-1207	[27]	**HBO**:Y101,R72 **HAL**:N65 **HPI**:F68,Y101 **PST**:F68 **SBR**:R41,R93	**SBR**:K17	
2ZOZ	ET-B-184	[28]	**HPI**:L59,L88,W63,W113,F147 **PST**:W63,F147	**PST**:W113,H153	**HPI**:L100,V92,I152
3O1H	TMO-B-1	[29]	**HBO**:W45 **PCT**:Y44 **WAT**:W45		
3PXF	2AN-A-305	[30]	**HBO**:D145,F146 **HPI**:L55,K56 **SBR**:K33	**HPI**:Y15,I35,V64,L66,L78	
	2AN-A-304	[30]	**HPI**:I52,L76 **SBR**:K56,H71	**HPY**:L78,V154,L37	
3R0T	FU9-A-338	[31]	**HBO**:V116 **HPI**:V66,F113,I174 **PST**:H160 **SBR**:K68 **WAT**:K68,W176	**HBO**:D175 **HPI**:L45,V53 **WAT**:D175	
3SHY	5FO-A-1	[32]	**HBO**:Q817 **HAL**:Y612 **HPI**:Y612 **PST**:F820	**HPI**:V782,I813,M816,F820	
3TAH	BGO-A-300	[33]	**HBO**:A11,K14,T15,S16,M114,A143,D113 **SBR**:D116 **WAT**:A11	**HBO**:S12,G13,N113,L144	
3T5Y	MCS-B-116	[34]	**HBO**:A327 **HPI**:R115 **SBR**:H295,R115	**HBO**:N117,G118	
3THY	ADP-A-935	[35]	**SBR**:K675		
4ALW	HY7-A-1308	[36]	**HBO**:D186 **SBR**:D186, E171		
4KYA	1UG-E-702	[37]	**HBO**:A609 **HPI**:I402,L516,F520,M608 **PST**:W403,F520 **SBR**:D513	**HBO**:Y553	
4PJT	2YQ-D-1104	[38]	**HBO**:G863 **PST**:Y889,Y907	**HBO**:Q759,E763	
4QNB	1B0-A-301	[39]	**HBO**:N57,K70 **PCT**:K70		
4RAO	3L7-B-301	[40]	**HBO**:R199,V187,K165,T141,K140,G139,T138,D137,R100,G69,K68 **PST**:F186 **WAT**:E133,D137,T141,M142,R199,G139		
4RDL	FUC-A-604	[41]	**HBO**:T347,G348,N395 **HPI**:W392 **WAT**:N395		

7 References

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