

Supporting Information for

Exhaustive repertoire of druggable cavities at protein-protein interfaces of known three-dimensional structure

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Table of contents

Table S1. Most frequent ligands in PPI cavities

Table S2. Set of rules implemented to filter PDB ligand by drug-likeness.

Table S3. Selection of best matching pairs between interfacial and sc-PDB cavities.

Table S4. Selection of best matching pairs between rim and sc-PDB cavities.

Table S5. Selection of best matching pairs between orthosteric and sc-PDB cavities.

Figure S1. Querying the PPIome database (<http://drugdesign.unistra.fr/ppiome>). **A)** Query example consisting in searching the database for protein-protein interfaces of known X-ray structure (resolution < 2 Å) for heterodimeric and non-enzymatic interfaces exhibiting druggable cavities larger than 500 Å³, of average buriedness higher than 90/120 and distant by less than 2 Å from the protein-protein interface. **B)** Results summary table.

Figure S2. Visualizing the interface between the ADP-ribosylation factor 1 (Arf1, chain A) and the Arf exchange factor (Arno, chain E) bound to the PPI stabilizer brefeldin A.

Figure S3. Distribution of molecular properties for ligands (drug-like, pharmacological tools) bound to druggable PPI cavities.

Figure S4. Distribution of the ligand globularity PBF score for PPI modulators (Interfacial, Rim, Allosteric, Orthosteric) bound to druggable cavities (this work), conventional drug-like ligands (sc-PDB) and PPI inhibitors (2P2IDB).

Table S1. Most frequent ligands in PPI cavities

HET	Class	Name	Frequency
Interfacial			
GOL	Reagent	Glycerol	197
EDO	Reagent	1,2-ethanediol	108
CL	Ion	Chloride ion	106
SO4	Ion	Sulfate ion	98
PLP	Prosthetic	Pyridoxal-5'-phosphate	97
ACT	Reagent	Acetate ion	64
FAD	Cofactor	Flavine-adenine dinucleotide	52
ATP	Cofactor	Adenosine-5'-triphosphate	46
LLP	Prosthetic	N'-Pyridoxyl-lysine-5'-monophosphate	45
PO4	Ion	Phosphate ion	40
Rim			
GOL	Reagent	Glycerol	2143
EDO	Reagent	1,2-ethanediol	1531
SO4	Ion	Sulfate ion	1419
CL	Ion	Chloride ion	691
PO4	Ion	Phosphate ion	654
FMN	Cofactor	Flavin mononucleotide	498
PLP	Prosthetic	Pyridoxal-5'-phosphate	478
FAD	Cofactor	Flavine-adenine dinucleotide	441
ACT	Ion	Acetate ion	425
NAD	Cofactor	Nicotinamide adenine dinucleotide	280
Allosteric			
NAD	Cofactor	Nicotinamide adenine dinucleotide	1043
SO4	Ion	Sulfate ion	1040
GOL	Reagent	Glycerol	865
NAP	Cofactor	Nicotinamide adenine dinucleotide phosphate	694
EDO	Reagent	1,2-ethanediol	686
FAD	Cofactor	Flavine-adenine dinucleotide	381
CL	Ion	Chloride ion	348
SAH	Tool	S-adenosyl-L-homocysteine	304
PO4	Ion	Phosphate ion	292
FMN	Cofactor	Flavin mononucleotide	289
Orthosteric			
GOL	Reagent	Glycerol	1827
SO4	Ion	Sulfate ion	1723
EDO	Reagent	1,2-ethanediol	1361
CL	Ion	Chloride ion	929
ZN	Metal	Zinc ion	751
PO4	Ion	Phosphate ion	728
FAD	Cofactor	Flavin-adenine dinucleotide	543
DOD	Water	Deuterated water	518
HEM	Organomet	Protoporphyrin IX containing Fe	405
ACT	Ion	Acetate ion	389

Table S2. Set of rules implemented in Filter (OpenEye Scientific software, Santa Fe, U.S.A) to filter PDB ligand by drug-likeness.

```

#/******
#Copyright (C) 2000-2005 by OpenEye Scientific Software, Inc.
#*****/
#This file defines the rules for filtering multi-structure files based on
#properties and substructure patterns.
MIN_MOLWT    150    "Minimum molecular weight"
MAX_MOLWT    750    "Maximum molecular weight"

MIN_NUM_HVY  10     "Minimum number of heavy atoms"
MAX_NUM_HVY  55     "Maximum number of heavy atoms"

MIN_RING_SYS 0     "Minimum number of ring systems"
MAX_RING_SYS 7     "Maximum number of ring systems"

MIN_RING_SIZE 0    "Minimum atoms in any ring system"
MAX_RING_SIZE 20   "Maximum atoms in any ring system"

MIN_CON_NON_RING 0  "Minimum number of connected non-ring atoms"
MAX_CON_NON_RING 20 "Maximum number of connected non-ring atoms"

MIN_FCNGRP   0     "Minimum number of functional groups"
MAX_FCNGRP   20    "Maximum number of functional groups"

MIN_UNBRANCHED 0  "Minimum number of connected unbranched non-ring atoms"
MAX_UNBRANCHED 8  "Maximum number of connected unbranched non-ring atoms"

MIN_CARBONS   5     "Minimum number of carbons"
MAX_CARBONS   40    "Maximum number of carbons"

MIN_HETEROATOMS 2  "Minimum number of heteroatoms"
MAX_HETEROATOMS 20  "Maximum number of heteroatoms"

MIN_Het_C_Ratio 0.10 "Minimum heteroatom to carbon ratio"
MAX_Het_C_Ratio 1.0  "Maximum heteroatom to carbon ratio"

MIN_HALIDE_FRACTION 0.0  "Minimum Halide Fraction"
MAX_HALIDE_FRACTION 0.5  "Maximum Halide Fraction"

#count ring degrees of freedom = (#BondsInRing) - 4 - (RigidBondsInRing) -
#(BondsSharedWithOtherRings)
#must be >= 0, from JCAMD 14:251-265,2000.
ADJUST_ROT_FOR_RING true  "BOOLEAN for whether to estimate degrees of freedom in rings"

MIN_ROT_BONDS 0     "Minimum number of rotatable bonds"
MAX_ROT_BONDS 20    "Maximum number of rotatable bonds"

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MIN_RIGID_BONDS 0 "Minimum number of rigid bonds"
MAX_RIGID_BONDS 50 "Maximum number of rigid bonds"

MIN_HBOND_DONORS 0 "Minimum number of hydrogen-bond donors"
MAX_HBOND_DONORS 6 "Maximum number of hydrogen-bond donors"

MIN_HBOND_ACCEPTORS 0 "Minimum number of hydrogen-bond acceptors"
MAX_HBOND_ACCEPTORS 10 "Maximum number of hydrogen-bond acceptors"

MIN_LIPINSKI_DONORS 0 "Minimum number of hydrogens on O & N atoms"
MAX_LIPINSKI_DONORS 5 "Maximum number of hydrogens on O & N atoms"

MIN_LIPINSKI_ACCEPTORS 0 "Minimum number of oxygen & nitrogen atoms"
MAX_LIPINSKI_ACCEPTORS 10 "Maximum number of oxygen & nitrogen atoms"

MIN_COUNT_FORMAL_CRG 0 "Minimum number formal charges"
MAX_COUNT_FORMAL_CRG 3 "Maximum number of formal charges"

MIN_SUM_FORMAL_CRG -2 "Minimum sum of formal charges"
MAX_SUM_FORMAL_CRG 2 "Maximum sum of formal charges"

MIN_CHIRAL_CENTERS 0 "Minimum chiral centers"
MAX_CHIRAL_CENTERS 4 "Maximum chiral centers"

MIN_XLOGP -2.0 "Minimum XLogP"
MAX_XLOGP 6.0 "Maximum XLogP"

#choices are insoluble<poorly<moderately<soluble<very<highly
MIN_SOLUBILITY moderately "Minimum solubility"

PSA_USE_SandP true "Count S and P as polar atoms"
MIN_2D_PSA 0.0 "Minimum 2-Dimensional (SMILES) Polar Surface Area"
MAX_2D_PSA 150.0 "Maximum 2-Dimensional (SMILES) Polar Surface Area"

AGGREGATORS true "Eliminate known aggregators"
PRED_AGG false "Eliminate predicted aggregators"

#secondary filters (based on multiple primary filters)
GSK_VEBER true "PSA>140 or >10 rot bonds"
MAX_LIPINSKI 2 "Maximum number of Lipinski violations"
MIN_ABS 0.5 "Minimum probability F>10% in rats"
PHARMACOPIA true "LogP > 5.88 or PSA > 131.6"

ALLOWED_ELEMENTS H,C,N,O,F,S,Cl,Br,I,P
ELIMINATE_METALS Sc,Ti,V,Cr,Mn,Fe,Co,Ni,Cu,Zn,Y,Zr,Nb,Mo,Tc,Ru,Rh,Pd,Ag,Cd

#acceptable molecules must have <= instances of each of the patterns below

#specific, undesirable functional groups

RULE 0 quinone
RULE 0 pentafluorophenyl_esters

```

RULE 0 paranitrophenyl_esters
RULE 0 HOBT_esters
RULE 0 triflates
RULE 0 lawesson_s_reagent
RULE 0 phosphoramides
RULE 0 beta_carbonyl_quat_nitrogen
RULE 0 acylhydrazide
RULE 0 cation_C_Cl_I_P_or_S
RULE 0 phosphoryl
RULE 0 alkyl_phosphate
RULE 0 phosphinic_acid
RULE 0 phosphanes
RULE 0 phosphoranes
RULE 0 imidoyl_chlorides
RULE 0 nitroso
RULE 0 N_P_S_Halides
RULE 0 carbodiimide
RULE 0 isonitrile
RULE 0 triacyloxime
RULE 0 cyanohydrins
RULE 0 acyl_cyanides
RULE 0 sulfonylnitrile
RULE 0 phosphorylnitrile
RULE 0 azocyanamides
RULE 0 beta_azo_carbonyl
RULE 0 polyenes
RULE 0 saponin_derivatives
RULE 0 cytochalasin_derivatives
RULE 0 cycloheximide_derivatives
RULE 0 monensin_derivatives
RULE 0 squalestatin_derivatives

#functional groups which often eliminate compounds from consideration

RULE 0 acid_halide
RULE 0 aldehyde
RULE 0 alkyl_halide
RULE 0 anhydride
RULE 0 azide
RULE 0 azo
RULE 0 di_peptide
RULE 0 michael_acceptor
RULE 0 beta_halo_carbonyl
RULE 0 nitro
RULE 0 oxygen_cation
RULE 0 peroxide
RULE 0 phosphonic_acid
RULE 0 phosphonic_ester
RULE 0 phosphoric_acid
RULE 0 phosphoric_ester
RULE 0 sulfonic_acid
RULE 0 sulfonic_ester

RULE 0 tricarbo_phosphene
RULE 0 epoxide
RULE 0 sulfonyl_halide
RULE 0 halopyrimidine
RULE 0 perhalo_ketone
RULE 0 aziridine
RULE 1 oxalyl
RULE 0 alphahalo_amine
RULE 0 halo_amine
RULE 0 halo_alkene
RULE 0 acyclic_NCN
RULE 0 acyclic_NS
RULE 0 SCN2
RULE 0 terminal_vinyl
RULE 0 hetero_hetero
RULE 0 hydrazine
RULE 0 N_methoyl
RULE 0 NS_beta_halothyl
RULE 0 propiolactones
RULE 0 iodoso
RULE 0 iodoxy
RULE 0 noxide

#groups of molecules

RULE 0 dye

#functional groups which are allowed, but may not be wanted in high quantities

#common functional groups

RULE 6 alcohol
RULE 8 alkene
RULE 4 amide
RULE 4 amino_acid
RULE 4 amine
RULE 4 primary_amine
RULE 4 secondary_amine
RULE 4 tertiary_amine
RULE 4 carboxylic_acid
RULE 6 halide
RULE 1 iodine
RULE 4 ketone
RULE 4 phenol
RULE 2 imine
RULE 1 methyl_ketone
RULE 1 alkylaniline
RULE 4 sulfonamide
RULE 1 sulfonylurea
RULE 0 phosphonamide
RULE 0 alphahalo_ketone
RULE 0 oxaziridine

RULE 1 cyclopropyl
RULE 2 guanidine
RULE 0 sulfonimine
RULE 0 sulfinimine
RULE 1 hydroxamic_acid
RULE 0 sulfinylthio
RULE 0 disulfide
RULE 0 enol_ether
RULE 0 enamine
RULE 0 organometallic
RULE 0 dithioacetal
RULE 1 oxime
RULE 0 isothiocyanate
RULE 0 isocyanate
RULE 3 lactone
RULE 3 lactam
RULE 1 thioester
RULE 1 carbonate
RULE 0 carbamic_acid
RULE 1 thiocarbamate
RULE 0 triazine
RULE 1 malonic

#other functional groups

RULE 2 alkyne
RULE 4 aniline
RULE 4 aryl_halide
RULE 4 carbamate
RULE 4 ester
RULE 4 ether
RULE 1 hydrazone
RULE 0 nonacylhydrazone
RULE 1 hydroxylamine
RULE 2 nitrile
RULE 2 sulfide
RULE 2 sulfone
RULE 2 sulfoxide
RULE 0 thiourea
RULE 1 thioamide
RULE 1 thiol
RULE 2 urea

RULE 0 hemiketal
RULE 0 hemiacetal
RULE 0 ketal
RULE 1 acetal
RULE 0 aminal
RULE 0 hemiaminal

#protecting groups

RULE 0 benzyloxycarbonyl_CBZ
RULE 0 t_butoxycarbonyl_tBOC
RULE 0 fluorenylmethoxycarbonyl_Fmoc
RULE 1 dioxolane_5MR
RULE 1 dioxane_6MR
RULE 1 tetrahydropyran_THP
RULE 1 methoxyethoxymethyl_MEM
RULE 2 benzyl_ether
RULE 2 t_butyl_ether
RULE 0 trimethylsilyl_TMS
RULE 0 t_butyldimethylsilyl_TBDMS
RULE 0 triisopropylsilyl_TIPS
RULE 0 t_butyldiphenylsilyl_TBDPS
RULE 1 phthalimides_PHT

Table S3. Selection of best matching pairs between interfacial and sc-PDB cavities.

Ref_PPI ^a	Fit-PDB ^b	Shape_sim ^c	Color_Sim ^d	SizeRef ^e	SizeFit ^f	DeltaSize ^g	RefName ^h	FitName ⁱ
4NKVAD8	2yhd	0.88	0.61	88	86	2.27	Steroid 17-alpha-hydroxylase/17,20 lyase	Androgen receptor
4NKVAD8	5dxg	0.94	0.62	88	97	9.28	Steroid 17-alpha-hydroxylase/17,20 lyase	Estrogen receptor Estrogen receptor Putative uncharacterized
4NKVAD8	2qgt	0.94	0.60	88	94	6.38	Steroid 17-alpha-hydroxylase/17,20 lyase	protein
4NKVAD8	1xow	0.93	0.62	88	86	2.27	Steroid 17-alpha-hydroxylase/17,20 lyase	Androgen receptor Estrogen receptor Nuclear receptor
4NKVAD8	3l03	0.97	0.60	88	97	9.28	Steroid 17-alpha-hydroxylase/17,20 lyase	coactivator 2
5SYMAB5	1nq0	0.86	0.63	91	92	1.09	Acyl-protein thioesterase 1	Thyroid hormone receptor beta
							Sensory rhodopsin-2 Sensory rhodopsin II	Estrogen receptor Nuclear receptor
5JJEAB4	4iu7	0.98	0.61	74	82	9.76	transducer	coactivator 2
							Sensory rhodopsin-2 Sensory rhodopsin II	
5JJEAB4	1u3q	0.95	0.62	74	81	8.64	transducer	Estrogen receptor beta
							Sensory rhodopsin-2 Sensory rhodopsin II	
5JJEAB4	1x7b	0.95	0.60	74	82	9.76	transducer	Estrogen receptor beta
3S2ZAB4	1eqh	0.91	0.61	71	77	7.79	cinnamoyl esterase; cinnamoyl esterase	Prostaglandin G/H synthase 1
3S2ZAB4	3pgh	0.94	0.63	71	76	6.57	cinnamoyl esterase; cinnamoyl esterase	Prostaglandin G/H synthase 2

^a PDB identifier_1st chain_2nd chain_cavity number, ^b PDB identifier of the sc-PDB entry, ^c shape similarity expressed by a Tversky coefficient, ^d pharmacophoric feature (color) similarity expressed by a Tversky coefficient, ^e number of features in the PPI cavity, ^f number of features in the sc-PDB cavity, ^g normalized difference in cavity sizes expressed in percentage, ^h UniProtKB name of the PPI entry, ⁱ UniProtKB name of the sc-PDB entry

Table S4. Selection of best matching pairs between rim and sc-PDB cavities.

Ref_PPI ^a	Fit-PDB ^b	Shape_sim ^c	Color_Sim ^d	SizeRef ^e	SizeFit ^f	DeltaSize ^g	RefName ^h	FitName ⁱ
4WFDGH2	5ikt	0.61	0.87	78	79	1.27	Exosome complex exonuclease RRP6; Exosome complex protein LRP1	Prostaglandin G/H synthase 2;
4H63FH2	1pzp	0.61	0.93	76	84	9.52	Mediator of RNA polymerase II transcription subunit 6; Mediator of RNA polymerase II transcription subunit 8	B-lactamase TEM;
3WFCBC4	4ok1	0.60	0.92	107	111	3.6	Nitric oxide reductase subunit B; Nitric oxide reductase subunit C;	Androgen receptor;
3SFYAB4	3sfx	0.64	0.96	137	135	1.46	Particulate methane monooxygenase α subunit; Particulate methane monooxygenase β subunit	Androgen receptor;
2ZQPYE7	1nq0	0.60	0.88	97	94	3.09	Protein translocase subunit SecY; Protein translocase subunit SecE	Thyroid hormone receptor β ;
2DD5GE1	1u3q	0.63	1.02	80	81	1.23	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Estrogen receptor β ;
2DD5GE1	4oil	0.61	0.98	80	82	2.44	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Androgen receptor;
2DD5GE1	3fl5	0.60	0.91	80	84	4.76	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Casein kinase II subunit α ;
2DD5GE1	4ofu	0.61	0.98	80	85	5.88	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Androgen receptor;
2DD5GE1	1yy4	0.62	0.97	80	85	5.88	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Estrogen receptor β ;
2DD5GE1	2am9	0.60	0.95	80	86	6.98	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Androgen receptor;
2DD5GE1	1t73	0.60	0.92	80	86	6.98	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Androgen receptor;
2DD5GE1	4l5m	0.62	0.92	80	86	6.98	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Cytohesin-2;
2DD4GE1	1nq0	0.61	0.93	87	94	7.45	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Thyroid hormone receptor β ;
2DD5GE1	1x76	0.61	0.93	80	87	8.05	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Estrogen receptor β ;

2DD4GE1	1nav	0.61	0.93	87	95	8.42	Thiocyanate hydrolase subunit α Thiocyanate hydrolase subunit β	Thyroid hormone receptor α ;
2DD5GE1	2piu	0.62	0.91	80	73	8.75	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Androgen receptor;
2DD5GE1	1qkm	0.62	0.91	80	73	8.75	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Estrogen receptor β ;
2DD5GE1	2xba	0.61	0.93	80	88	9.09	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	ALK tyrosine kinase receptor;
2DD5GE1	3lps	0.60	0.94	80	88	9.09	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	DNA topoisomerase 4 subunit B;
2DD5GE1	1x78	0.61	0.98	80	88	9.09	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Estrogen receptor β ;
2DD4GE1	1nax	0.61	0.99	87	96	9.38	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit β	Thyroid hormone receptor β ;
4O4HCB7	4nh0	0.61	0.90	87	88	1.14	Tubulin α -1B chain; Tubulin β -2B chain	ESX secretion system protein EccC;

^a PDB identifier_1st chain_2nd chain_cavity number, ^b PDB identifier of the sc-PDB entry, ^c shape similarity expressed by a Tversky coefficient, ^d pharmacophoric feature (color) similarity expressed by a Tversky coefficient, ^e number of features in the PPI cavity, ^f number of features in the sc-PDB cavity, ^g normalized difference in cavity sizes expressed in percentage, ^h UniProtKB name of the PPI entry, ⁱ UniProtKB name of the sc-PDB entry

Table S5. Selection of best matching pairs between orthosteric and sc-PDB cavities.

Ref_PPI ^a	Fit-PDB ^b	Shape_sim ^c	Color_Sim ^d	SizeRef ^e	SizeFit ^f	DeltaSize ^g	RefName ^h	FitName ⁱ
2UGI12J8XCD	5ikt	0.86	0.60	76	79	3.8	Uracil-DNA glycosylase inhibitor	Prostaglandin G/H synthase 2
2UGI12J8XCD	3s0d	0.82	0.60	76	77	1.3	Uracil-DNA glycosylase inhibitor	OBP14
2UGI12J8XCD	2if8	0.75	0.62	76	82	7.32	Uracil-DNA glycosylase inhibitor	Inositol polyphosphate multikinase
2UGI12J8XCD	1pzp	0.85	0.62	76	84	9.52	Uracil-DNA glycosylase inhibitor	Beta-lactamase TEM
2UGI12ZHAB	4ofu	0.79	0.60	80	85	5.88	Uracil-DNA glycosylase inhibitor	Androgen receptor
2UGI12ZHAB	3s0d	0.80	0.60	80	77	3.75	Uracil-DNA glycosylase inhibitor	OBP14
2UGI12ZHAB	1pzp	0.85	0.60	80	84	4.76	Uracil-DNA glycosylase inhibitor	Beta-lactamase TEM
2UGI12ZHAB	1t7t	0.84	0.60	80	85	5.88	Uracil-DNA glycosylase inhibitor	Androgen receptor

^a PDB identifier of the monomeric protein_cavity number_PDB identifier of the matched dimer_1st chain_2nd chain, ^b PDB identifier of the sc-PDB entry, ^c shape similarity expressed by a Tversky coefficient, ^d pharmacophoric feature (color) similarity expressed by a Tversky coefficient, ^e number of features in the PPI cavity, ^f number of features in the sc-PDB cavity, ^g normalized difference in cavity sizes expressed in percentage, ^h UniProtKB name of the PPI entry, ⁱ UniProtKB name of the sc-PDB entry

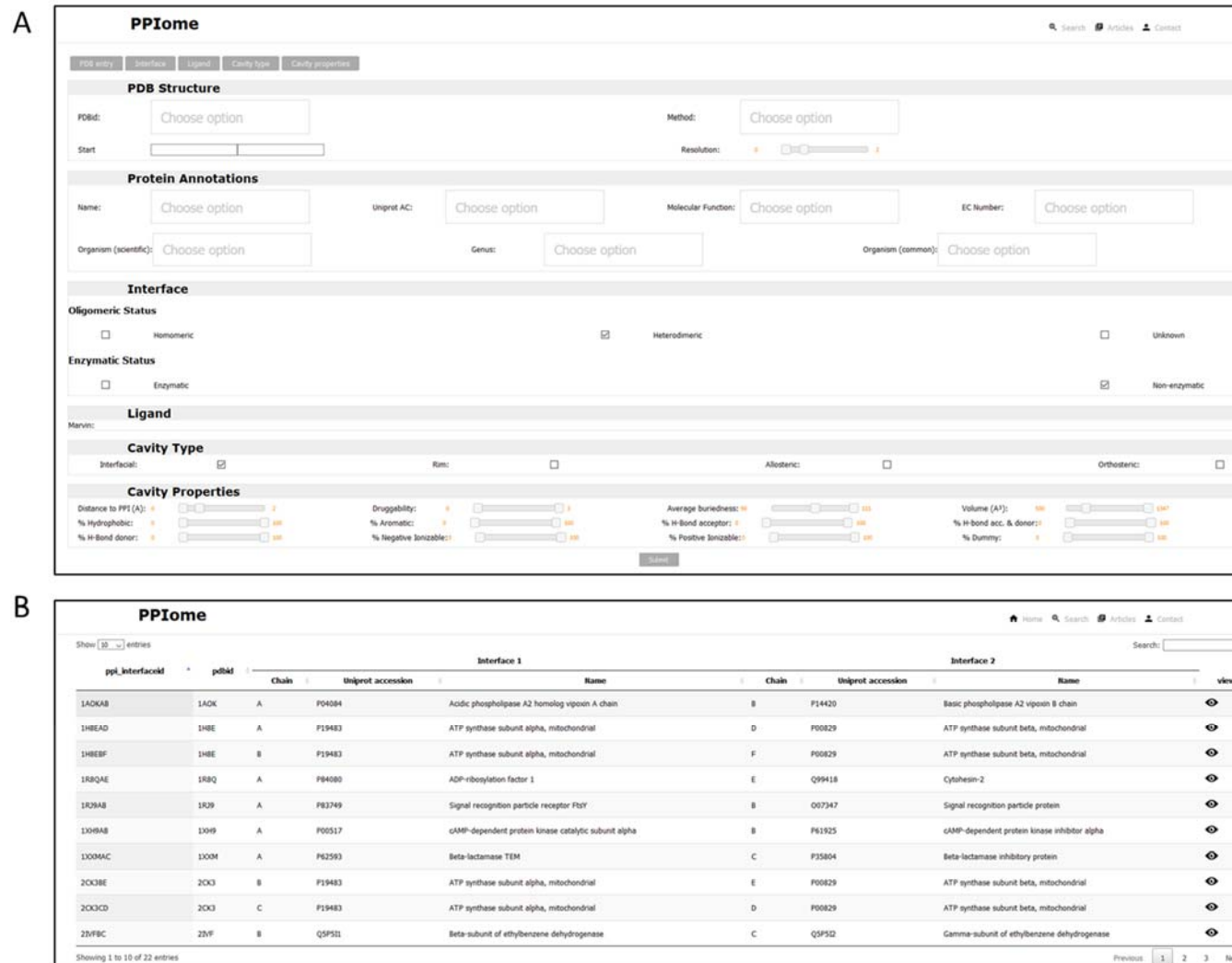


Figure S1. Querying the PPIome database (<http://drugdesign.unistra.fr/ppiome>). **A)** Query example consisting in searching the database for protein-protein interfaces of known X-ray structure (resolution < 2 Å) for heterodimeric and non-enzymatic interfaces exhibiting druggable cavities larger than 500 Å³, of average buriedness higher than 90/120 and distant by less than 2 Å from the protein-protein interface. **B)** Results summary table.

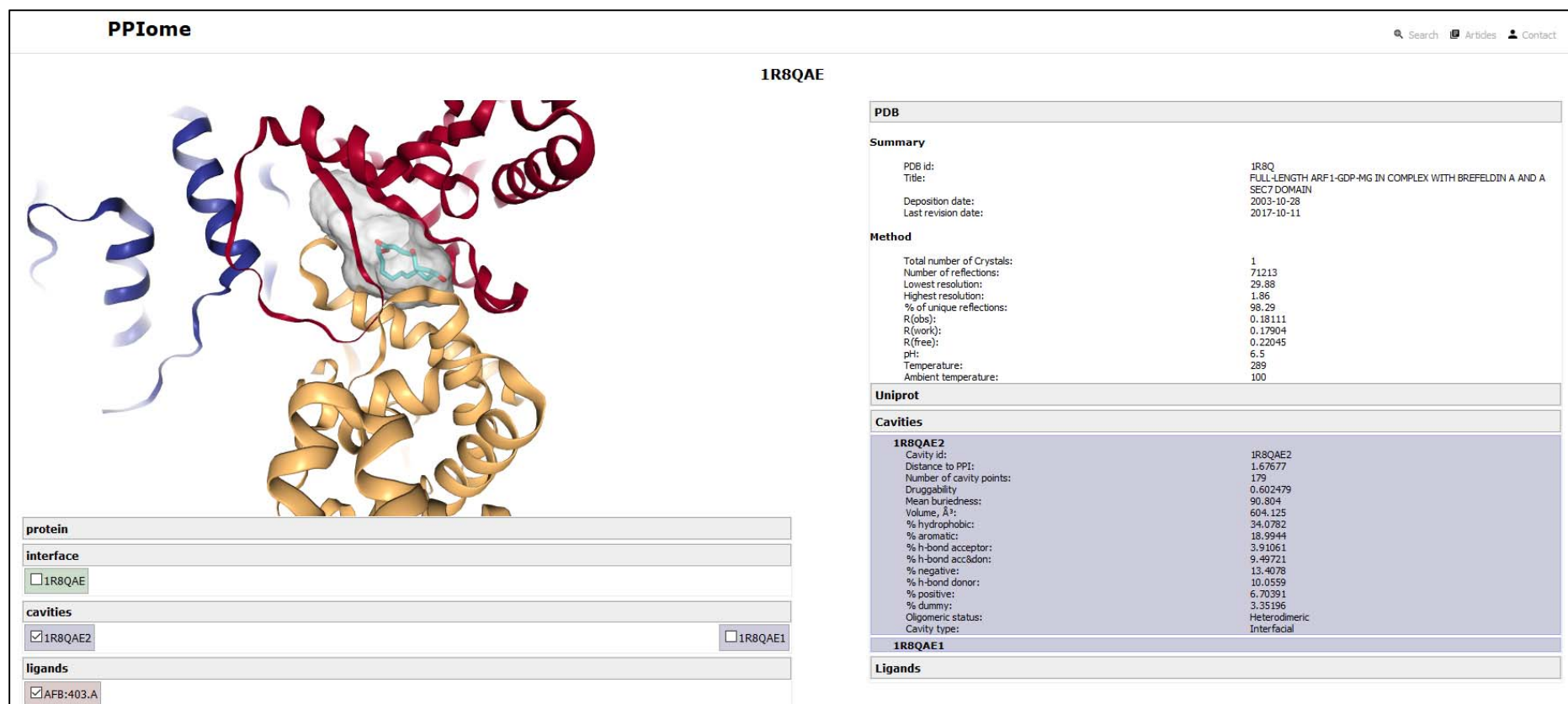


Figure S2. Visualizing the interface between the ADP-ribosylation factor 1 (Arf1, chain A, red ribbons) and the Arf exchange factor (Arno, chain E, yellow ribbons) bound to the PPI stabilizer brefeldin A (cyan sticks, PDB entry 1R8Q).

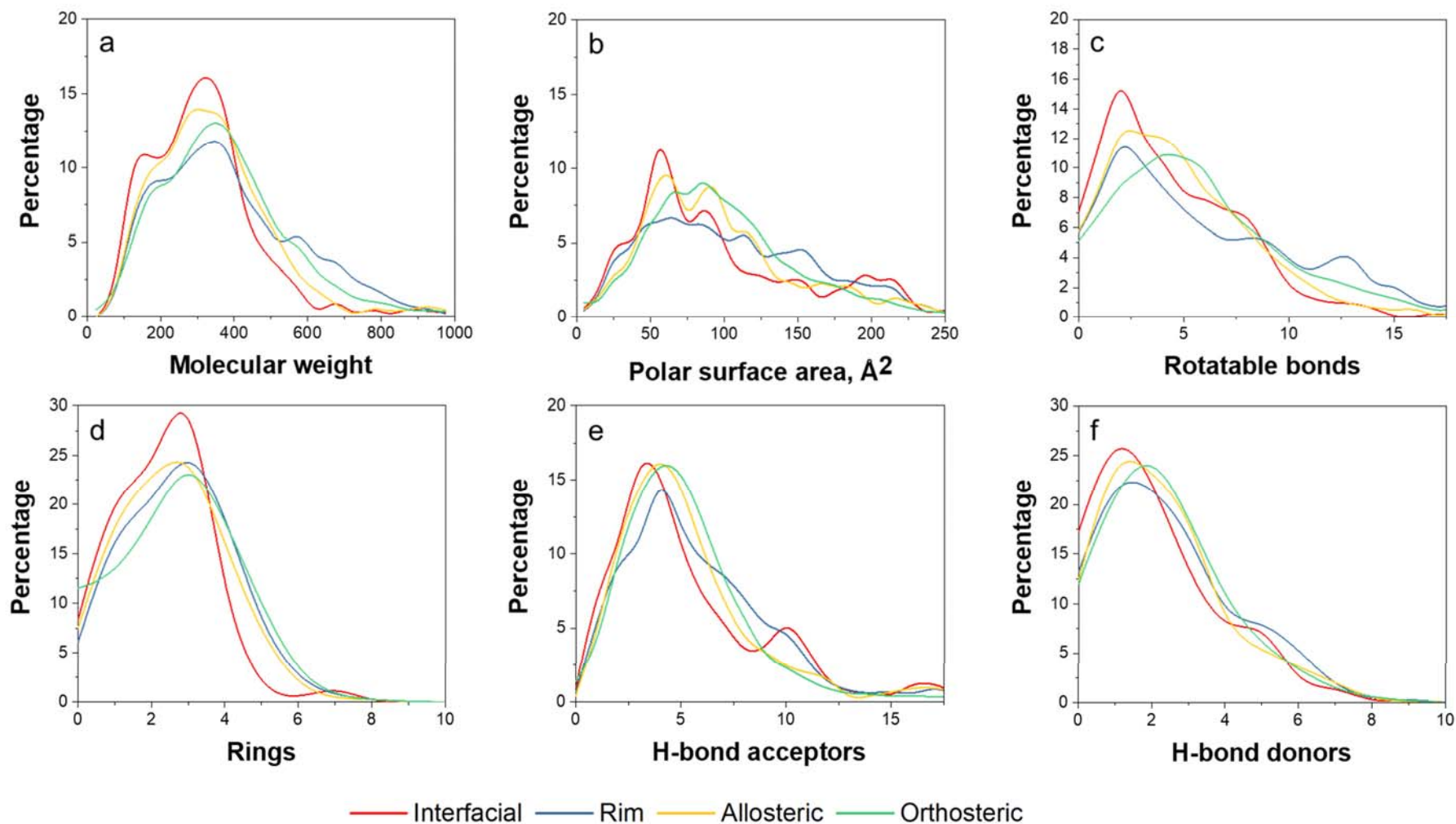


Figure S3. Distribution of molecular properties for ligands (drug-like, pharmacological tools) bound to druggable PPI cavities. **(a)** Molecular weight (Da), **(b)** topological polar surface area (Å²), **(c)** Number of rotatable bonds, **(d)** Number of rings, **(e)** Number of hydrogen bond acceptors, **(f)** Number of hydrogen bond donors.

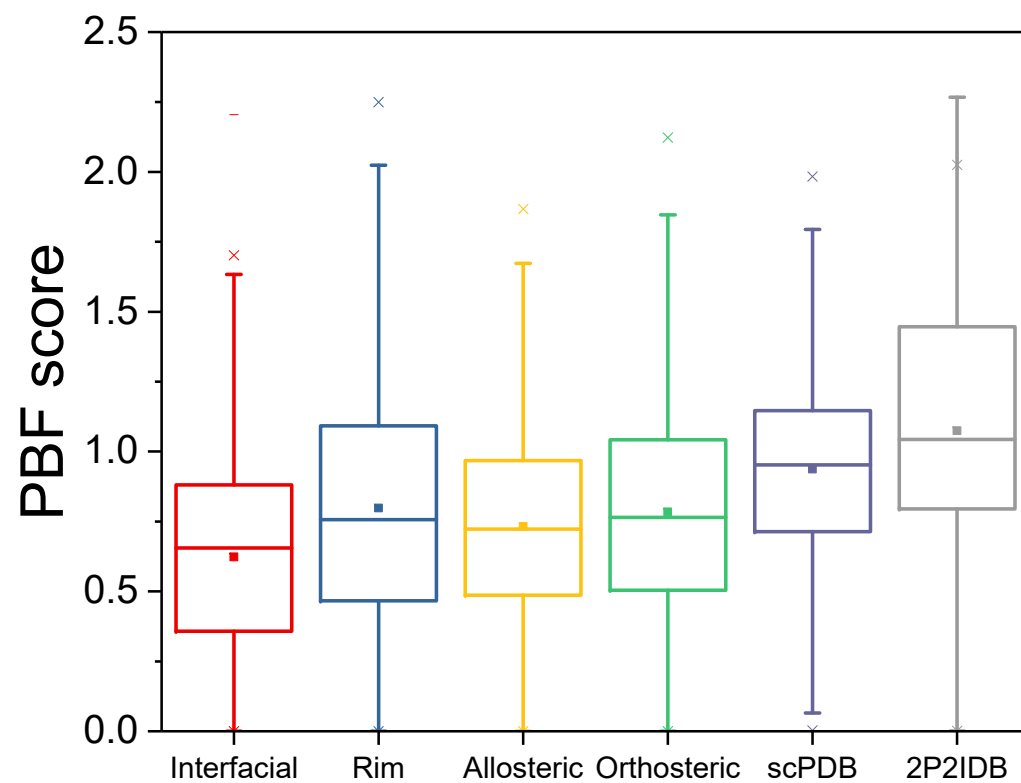


Figure S4. Distribution of the ligand globularity PBF score for PPI modulators (Interfacial, Rim, Allosteric, Orthosteric) bound to druggable cavities (this work), conventional drug-like ligands (sc-PDB) and PPI inhibitors (2P2IDB).