Supporting Information for

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

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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).

HET	Class	Name	Frequency
Interfacial			. <u>,</u>
GOL	Reagent	Glycerol	197
EDO	Reagent	, 1.2-ethanediol	108
CL	lon	Chloride ion	106
504	lon	Sulfate ion	98
PIP	Prosthetic	Pyridoxal-5'-phosphate	97
ACT	Reagent	Acetate ion	64
FAD	Cofactor	Flavine-adenine dunucleotide	52
ATP	Cofactor	Adenosine-5'-triphosphate	46
IIP	Prosthetic	N'-Pyridoxyl-lysine-5'-mononhosphate	45
PO4	Ion	Phosphate ion	40
104	1011	i nospirate ion	40
Rim			
GOL	Reagent	Glycerol	2143
EDO	Reagent	1,2-ethanediol	1531
SO4	lon	Sulfate ion	1419
CL	lon	Chloride ion	691
PO4	lon	Phosphate ion	654
FMN	Cofactor	Flavin mononucleotide	498
PLP	Prosthetic	Pyridoxal-5'-phosphate	478
FAD	Cofactor	Flavine-adenine dinucleotide	441
ACT	lon	Acetate ion	425
NAD	Cofactor	Nicotinamide adenine dinucleotide	280
Allosteric			
NAD	Cofactor	Nicotinamide adenine dinucleotide	1043
SO4	lon	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	lon	Chloride ion	348
SAH	Tool	S-adenosyl-L-homocysteine	304
PO4	lon	Phosphate ion	292
FMN	Cofactor	Flavin mononucleotide	289
Orthosteric			
GOL	Reagent	Glycerol	1827
SO4	lon	Sulfate ion	1723
	Reagent	1 2-ethanediol	1361
	lon	Chloride ion	020
2L 7N	Motal	Zinc ion	529 751
		Phosphate ion	107 סרד
	Cofactor	Elavin-adonino dinucleotido	720
		Doutorated water	543
	VValer	Deuteraleu Waler Drotonornhurin IV containing Fo	518
	Organomet		405
ACI	ion	Acetate Ion	389

Table S1. Most frequent ligands in PPI cavities

 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" "Maximum molecular weight" MAX_MOLWT 750 MIN NUM HVY 10 "Minimum number of heavy atoms" MAX NUM HVY 55 "Maximum number of heavy atoms" MIN RING SYS 0 "Minumum number of ring systems" MAX RING SYS 7 "Maximum number of ring systems" MIN_RING_SIZE 0 "Minimum atoms in any ring system" "Maximum atoms in any ring system" MAX_RING_SIZE 20 MIN_CON_NON_RING 0 "Minimum number of connected non-ring atoms" MAX_CON_NON_RING 20 "Maximum number of connected non-ring atoms" "Minimum number of functional groups" MIN FCNGRP 0 MAX FCNGRP "Maximum number of functional groups" 20 MIN UNBRANCHED 0 "Minimum number of connected unbranched non-ring atoms" MAX UNBRANCHED 8 "Maximum number of connected unbranched non-ring atoms" "Minimum number of carbons" MIN_CARBONS 5 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" "Minimum Halide Fraction" MIN HALIDE FRACTION 0.0 MAX_HALIDE_FRACTION "Maximum Halide Fraction" 0.5 #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"

MIN RIGID BONDS 0 "Minimum number of rigid bonds" "Maximum number of rigid bonds" MAX_RIGID_BONDS 50 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" "Minimum number of hydrogens on O & N atoms" MIN LIPINSKI DONORS 0 "Maximum number of hydrogens on O & N atoms" MAX_LIPINSKI_DONORS 5 "Minimum number of oxygen & nitrogen atoms" MIN LIPINSKI ACCEPTORS 0 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" "Maximum sum of formal charges" MAX_SUM_FORMAL_CRG 2 MIN_CHIRAL_CENTERS 0 "Minimum chiral centers" MAX CHIRAL CENTERS 4 "Maximum chiral centers" "Minimum XLogP" MIN XLOGP -2.0 MAX_XLOGP 6.0 "Maximum XLogP" #choices are insoluble<poorly<moderately<soluble<very<highly</pre> MIN_SOLUBILITY moderately "Minimum solubility" PSA_USE_SandP true "Count S and P as polar atoms" "Minimum 2-Dimensional (SMILES) Polar Surface Area" MIN_2D_PSA 0.0 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) "PSA>140 or >10 rot bonds" GSK VEBER true MAX_LIPINSKI 2 "Maximum number of Lipinski violations" "Minimum probability F>10% in rats" MIN_ABS 0.5 PHARMACOPIA true "LogP > 5.88 or PSA > 131.6" ALLOWED ELEMENTS H,C,N,O,F,S,CI,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 sulfonyInitrile RULE 0 phosphonylnitrile 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

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	3103	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

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

^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

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 eta	Estrogen receptor β;
2DD5GE1	4oil	0.61	0.98	80	82	2.44	Thiocyanate hydrolase subunit α ; Thiocyanate hydrolase subunit eta	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	1уу4	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;

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

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 ;
404HCB7	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

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
2UGI12ZHXAB	4ofu	0.79	0.60	80	85	5.88	Uracil-DNA glycosylase inhibitor	Androgen receptor
2UGI12ZHXAB	3s0d	0.80	0.60	80	77	3.75	Uracil-DNA glycosylase inhibitor	OBP14
2UGI12ZHXAB	1pzp	0.85	0.60	80	84	4.76	Uracil-DNA glycosylase inhibitor	Beta-lactamase TEM
2UGI12ZHXAB	1t7t	0.84	0.60	80	85	5.88	Uracil-DNA glycosylase inhibitor	Androgen receptor

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

^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, ¹ UniProtKB name of the sc-PDB entry

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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).